STRATEGIES TOWARDS THE SYNTHESIS OF PROSTAGLANDIN ANALOGUES

BY

HAYLEY CLAIRE HAUPT

Thesis
Presented for the Degree of
DOCTOR OF PHILOSOPHY

In the
Department of Chemistry
University of Cape Town

APRIL 2006

ABSTRACT

Different strategies for the synthesis of cyclopentenone prostaglandins and their analogues have been explored. The key transformation critical to the success of each of the described routes involves a Lewis-acid mediated retro Diels-Alder (rDA) reaction as the final step in liberating a 4, 5 disubstituted cyclopent-2-ene-1-one under extremely mild conditions. The first approach involves installation of the α-chain followed by base-mediated methodology to affect regiospecific enolate generation. Effective trapping of the enolate generates the requisite target. Within the context of this strategy both 2- and 3-component coupling protocols have been elaborated. Having demonstrated that the α- and β- sidechains could be installed, the key rDA reaction has been used to generate target analogues.

The second approach utilizes a Diels-Alder cycloaddition reaction as the key step. The thermal and Lewis-acid catalysed Diels-Alder reactions between tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one and 3-hydroxytricyclo[5.2.1.$0^{2,6}$]dec-8-ene with butadiene and butadiene sulfone have been investigated. While reaction between the enone and the dienophiles proved to be low yielding, the reaction between the allylic alcohol and butadiene sulfone proceeded readily and in high yield. The derived cycloadduct represents a late-stage intermediate for the synthesis of isoprostanes. Methodologies to perform cis-hydroxylation followed by oxidative cleavage of the cyclohexene moiety have been successfully implemented.

Finally, a synthesis was designed for generating oxygen analogues of the prostaglandin targets. This involved the generation of (3-*exo*, 4-*endo*)-5-oxatetracyclo[6.2.1.0.$^{2,7}0^{4,6}$]undec-9-en-3-ol. Nucleophilic epoxide opening formed the basis for the installation oxygen on the ring. Methods for the succesful synthesis of both *exo* and *endo* epoxides of this nature have been demonstrated and the comparative opening of both structures has been investigated with the *endo*-epoxide producing the most promising results.

CONTENTS

CHAPTER 1

INTRODUCTION

1.1. Background:

Prostaglandins (PG's) are a group of naturally occurring compounds that are generated *in vivo* from arachidonic acid *via* the membrane-bound cyclooxegenase enzyme system. [1, 2,3]

The central structural element of PG's is prostanoic acid (Figure 1.1). There are several different types of PG's comprising the prostaglandin alphabet and they are classified alphabetically from A-J (Figure 1.2). The letters identify the functional groups of the cyclopentane ring with a three-numerical subscript series indicating the number of double bonds in the sidechains. The PGF family (Figure 1.2) is further subdivided by means of a subscript α and β to distinguish the relative configuration of the hydroxyl group at position 9.

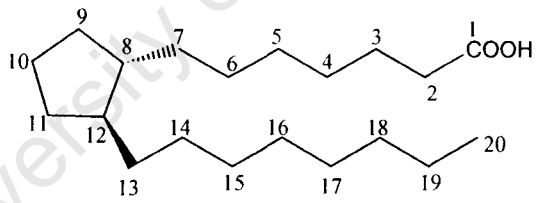
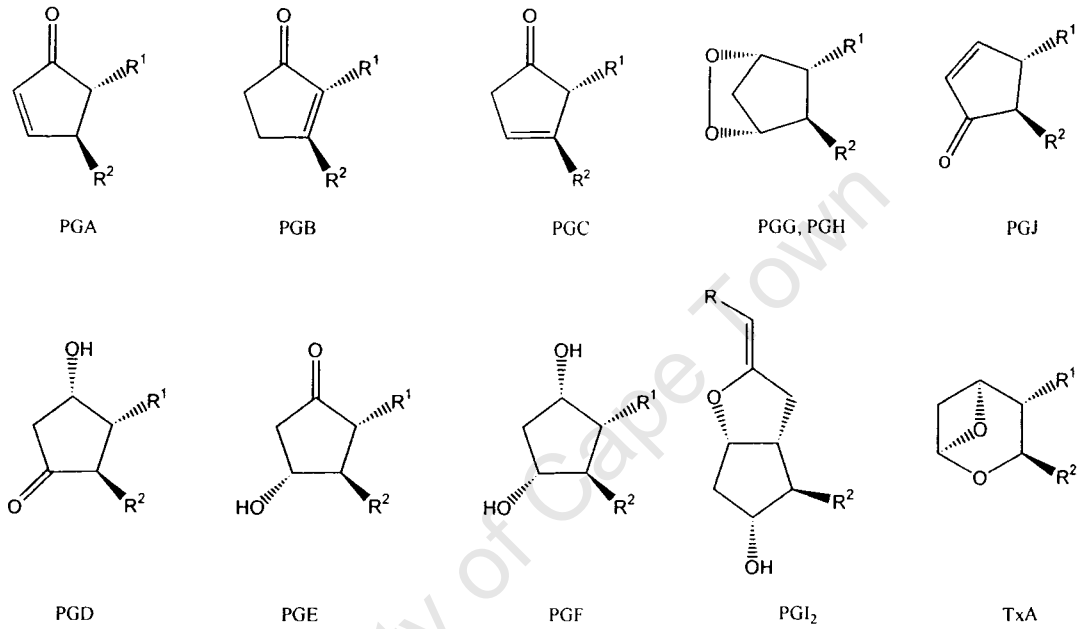


Figure 1.1

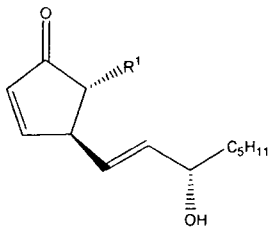
These primary prostaglandins and their analogues display a broad spectrum of biological activities, which renders specific target selectivity difficult to achieve. Nevertheless, some such compounds have proved to be commercially viable. For example, Limaprost [4] has proved to be a successful drug for the treatment of gastrointestinal problems while Mexiprostil [5], whose synthesis is described below (Scheme 1.2), is used for the treatment of cardiovascular disease.



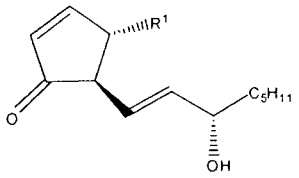
PG_1 series, $R^1 = (CH_2)_6CO_2H$; PG_2 series, $R^1 = CH_2CH{=}CH(CH_2)_3CO_2H$, *Z*-alkene, $R^2 = CH{=}CHCH(OH)C_5H_{11}$ (*S* configuration) except for PGG when $R^2 = CH{=}CHCH(OOH)C_5H_{11}$

Figure 1.2 The prostaglandin alphabet.

Cyclopentenone prostaglandins, cyPG's, (prostaglandins of the A and J series Figure 1.3) have been shown to inhibit viral replication and hence have emerged as a new class of potentially therapeutic agents.[6]



1



2

PGA_1 $R^1 = (CH_2)_6CO_2H$

PGA_2 $R^1 = CH_2CH{=}CH(CH_2)_3CO_2H$ (Z)

PG-J1α

PG-J2α

Figure 1.3

They exhibit at least a component of their activity by induction of heat shock protein synthesis [7](*via* activation of Heat Shock Factor (HSF)) and inhibition of the nuclear transcription factor NF-κB (Figure 1.4).[8-9] Heat-shock proteins (HSP) are known to protect mammalian cells against a wide range of toxic conditions, including extreme temperatures, oxidative stress, exposure to heavy metals or cytotoxic drugs, glucose deprivation and viral infection. This defence mechanism involves producing large amounts of these proteins which have a cytoprotective function. It requires the activation and translocation of HSF to the nucleus. HSF exists in an inactive, non-DNA binding form. Upon exposure of the cell to heat shock or other stimuli, it is rapidly converted into the DNA binding.[10] In the nucleus, it then binds to specific heat shock elements and activates transcription. Cyclopentenone PG's are potent activators of HSF.

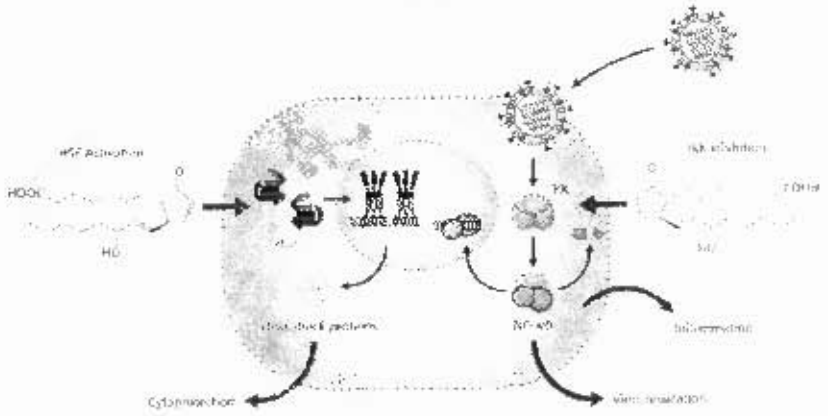


Figure 1.4

The second mode of activity is exhibited in the suppression of the nuclear transcription factor NF-κB.

NF-κB is a regulator of the immediate early pathogen response and the activation of the immune system. It is known to play a critical role in the regulation of the body's inflammatory and immune responses. This transcription factor exists as part of an inactive cytoplasmic complex (called IKK). In the complex it is bound to an inhibitory protein of the IκB family, usually IκBα, and is activated in response to pathogenic stimuli. Stimulation triggers phosphorylation of the IKK complex, degrading IκBα which results in NF–κB translocation to the nucleus. In the nucleus, NF-κB binds to DNA inducing a variety of genes encoding signalling proteins. Inhibiting NF-κB suppresses the synthesis of viral proteins. Cyclopentenone prostaglandins suppress NF-κB by inhibiting the kinase enzyme IKK responsible for NF-κB activation.

These cyclopentenone PG's have been shown to inhibit a range of viruses including poliovirus and human immunodeficiency virus (HIV) *via* the cytoprotective activity mentioned above.[11-13]

The cyclopentenone ring structure is key to their activity and serves as a Michael acceptor involved in reacting with thiol groups of key proteins. [14]

Another series of prostaglandin-like compounds, with interesting biological properties, which have emerged are the isoprostanes.[15,16] Isoprostanes are the products of a non-enzymatic free radical initiated peroxidation arachidonic acid in the mammalian cell. This contrasts with the cycooxygenase mediated process for the formation of PG's. They hence serve as markers of oxidative stress.[17,18] They have also been shown to be potent vasoconstrictors as well as platelet aggregation factors[19] and while little is really known of their biological activity, their increased formation during kidney failure and severe liver disease has been reported.[20] Isoprostanes A and J are the C12- and C8-epimers of PG's of the A and J series respectively (Figure 1.5). Isoprostanes can be distinguished from other PG's by two structural features, firstly the thermodynamically less stable *cis*-stereochemistry of the two sidechains and secondly, that they are generated in racemic form which is consistent with a non-enzymatic radical mediated pathway.[21] Isoprostanes of the A_2 and J_2 series have been shown to be active against a range DNA and RNA viruses, including HIV-1 and influenza virus. They are generated through dehydration of E_2 and D_2 isoprostanes respectively.

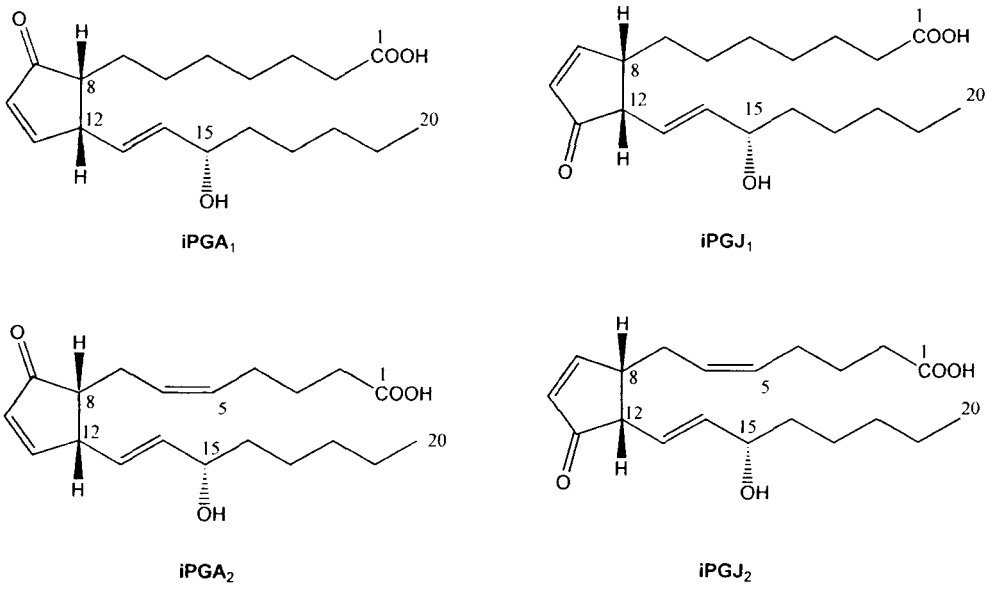


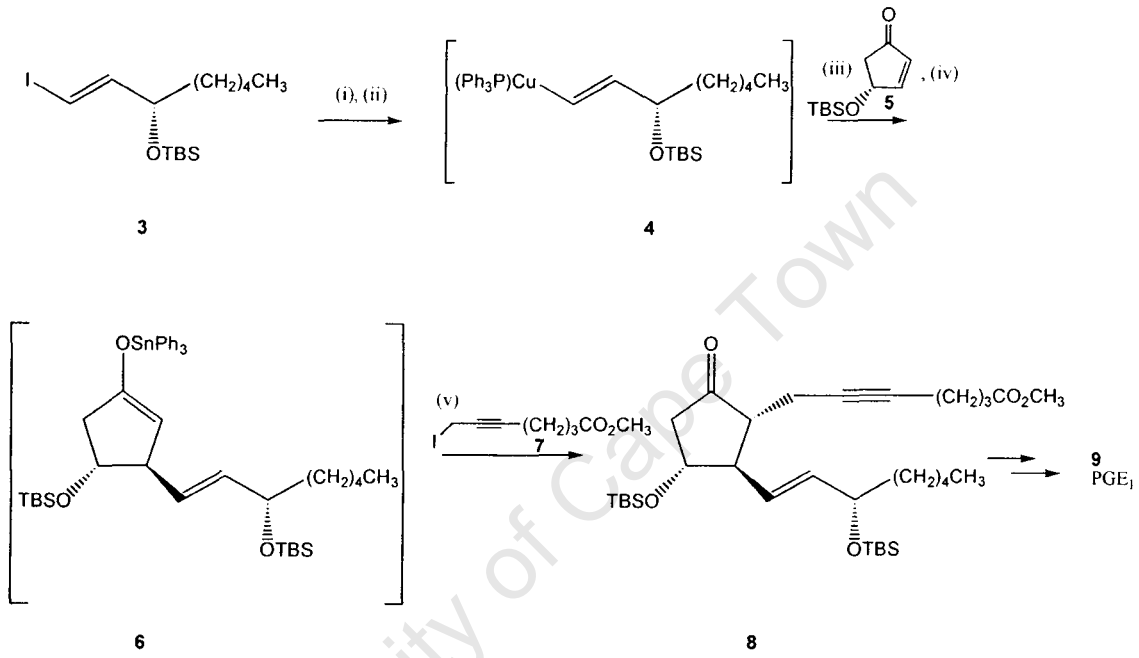
Figure 1.5 Isoprostanes of the A and J series.

1.2. Synthesis of cyclopentenone prostaglandins

Cyclopentenone PG's emerged as an attractive class of prostanoids in the early 1990's. To date, there have been a number of synthetic approaches to these analogues with the most popular methodology being Nyori's three component coupling (3CC) approach. This multicomponent coupling strategy involves a "one-pot" process that combines three or more substrates simultaneously. Hence, this constitutes a direct route to PG's.

Nyori's three component strategy has been one of the most widely utilized strategies for accessing *trans*-1,2-substituted cyclopentane PG's and was initially designed to gain access to the PGE series. The strategy involves a tandem conjugate addition to a cyclic enone followed by trapping of the resulting enolate with a reactive electrophile. The general strategy makes use of organocuprates in the conjugate addition phase and proceeds smoothly with cyclopentenones. However, trapping of the lithium enolate proved low-yielding. This has been attributed in large part to enolate equilibration. [22] This led, over

time, to the investigation of the efficiency of a number of alternative metal-enolates, generated either by the nature of the conjugate addition adduct or *via* a transmetallation of the generated enolate. Tin enolates were found to be successful as exemplified in the synthesis of PGE_1. In this example, a phosphine-complexed organocuprate is transmetallated with triphenyltin chloride to give the tin enolate under conditions which utilize HMPA (Scheme 1.1).

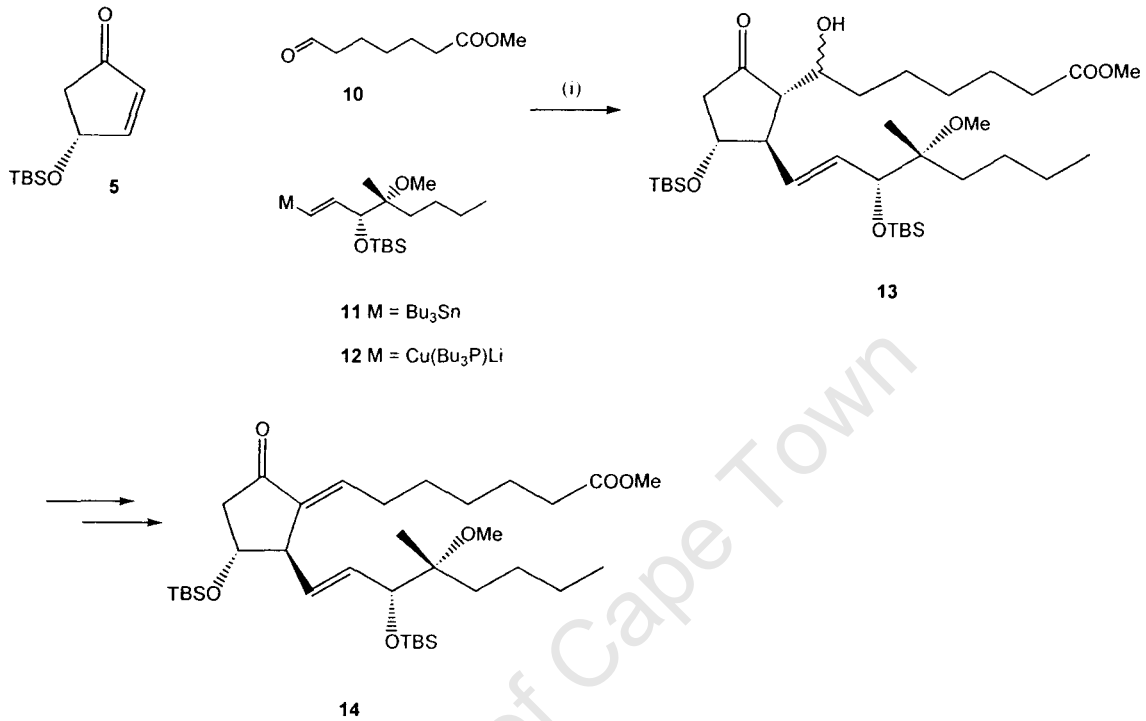


Scheme 1.1 *Reagents and conditions*: (i) *t*-BuLi, Et_2O, -95 to -78°C, 3 h, (ii) CuI, PPh_3, THF, -78°C, 10 min, (iii) **5**, THF, -78°C, (iv) HMPA, Ph_3SnCl, (v) **7** in HMPA, -30 °C, 39 h.

The use of triorganozinc allowed the process to occur through a zinc enolate intermediate. This resulted in comparable yields to those of the organocopper route but isolation of the product was easier. The use of dimethylzinc eliminated the need for the phosphine/copper complex or triphenyltin chloride.[23]

The multigram preparation of Mexiprostil (Scheme1.2) uses the vinylstannane of the lower side chain **11**. The vinylstannane is treated with *n*-BuLi and copper

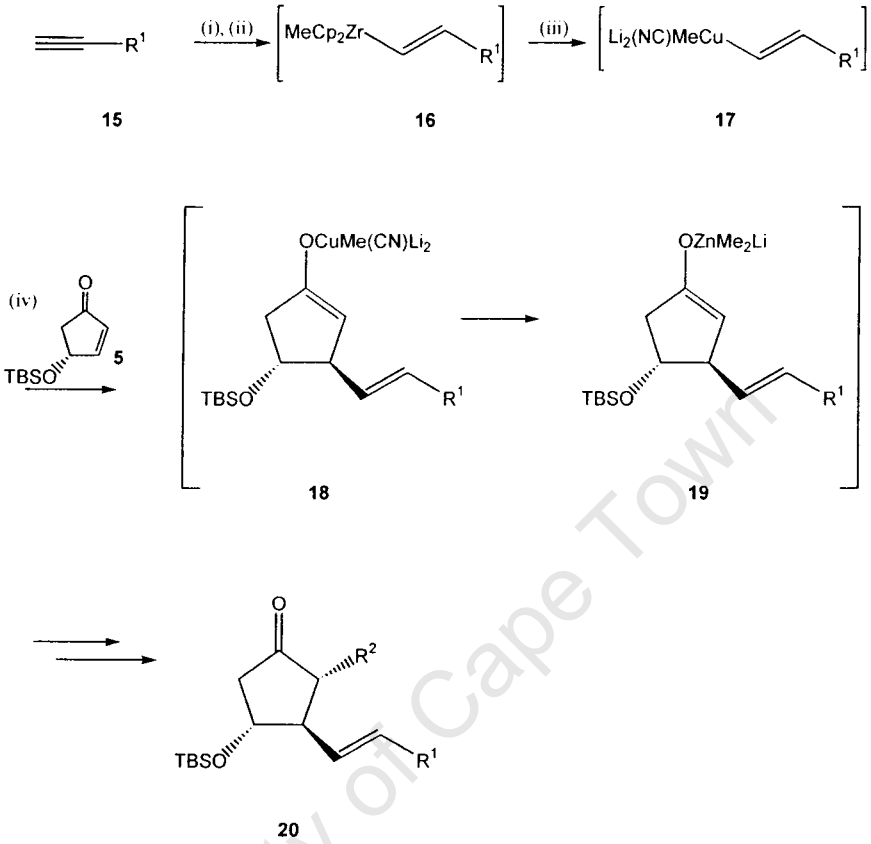
iodide to afford the organocopper reagent **(12)**. Sequential treatment of the enone with the cuprate **(12)** and aldehyde **(10)** gave a mixture of diastereomers of the hydroxyl PGE_1 derivative **(14)**.



Scheme 1.2 *Reagents and conditions*: (i) *n*-BuLi, Bu_3P, CuI, **11**, -78°C, 50%.

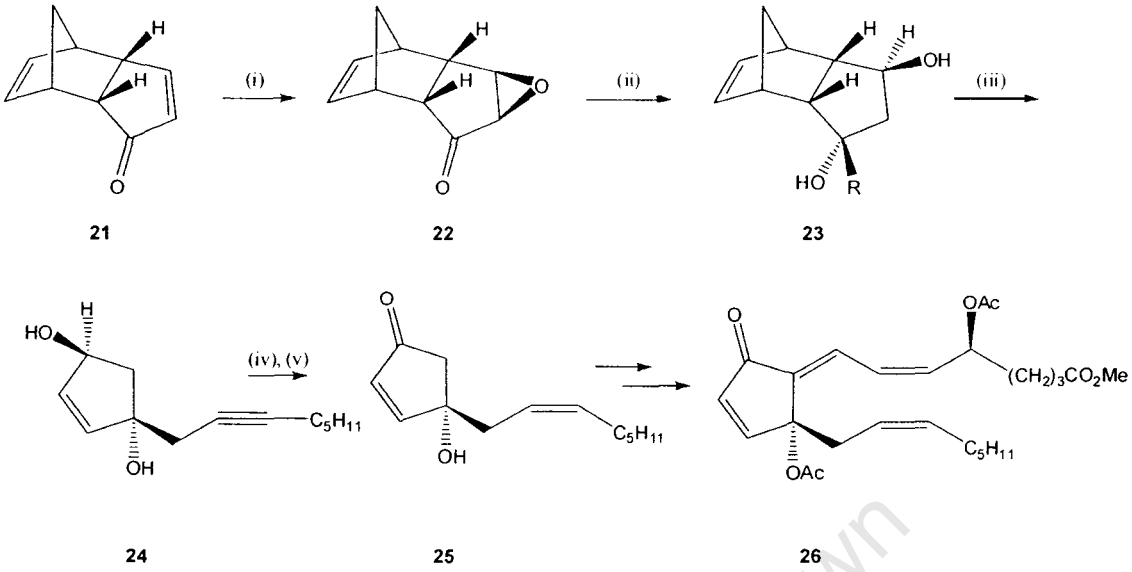
Lipshutz and Wood have described the use of a zincate reagent Bu_3ZnLi to produce a reactive zinc enolate in the synthesis of PG analogues (Scheme 1.3). They had previously demonstrated alkyne hydrozirconation to a cyclopentenone and *in situ* transmetallation to generate a higher order cyanocuprate. Following this, attempts at transmetallation and ensuing conjugate addition with the zincate reagent was attempted. Following hydrozirconation of the alkyne **(15)**, the Zr-Cl bond is substituted with MeLi to give **17**. Transmetallation with a catalytic amount of the cyanocuprate $Me_2Cu(CN)Li_2$ in the presence of the zincate reagent with slow enone **(5)** addition, leads to the conjugate addition product **(18)** which is transformed *via*

Cu-to-Zn transmetallation to the zinc enolate **(19)**. The electrophile then traps the enolate to generate the three component coupling product **(20)**.



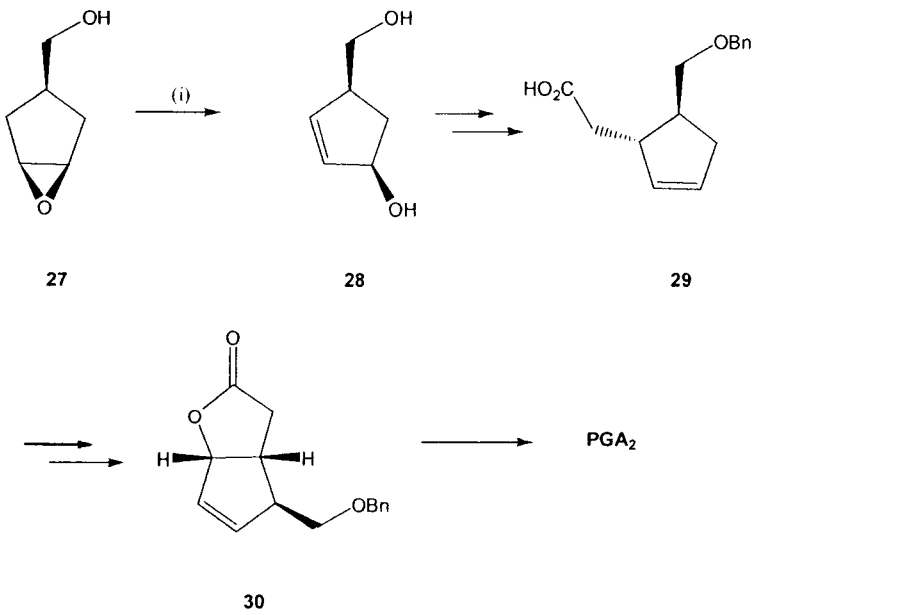
Scheme 1.3 *Reagents and conditions*: (i) Cp_2ZrHCl, THF, rt, (ii) MeLi, -78°C, (iii) $Me_2Cu(CN)Li_2$, MeLi, Me_3ZnLi, (iv) **18**, slow addition at -78°C, (v) R^2CHO or R^2OTf, -78°C.

Zwannenburg *et al* described the enantio- and stereoselective synthesis of clavulone **(26)** form the PG intermediate γ-hydroxycyclopentenone **(24)** (Scheme 1.4).[24] Nucleophilic octynylzinc addition to the carbonyl group of **22** was followed by reductive opening of the oxirane. Cycloreversion of **23**, selective oxidation of the secondary hydroxyl group and reduction of the alkyne moiety afforded **25** from which **26** was obtained in three steps.



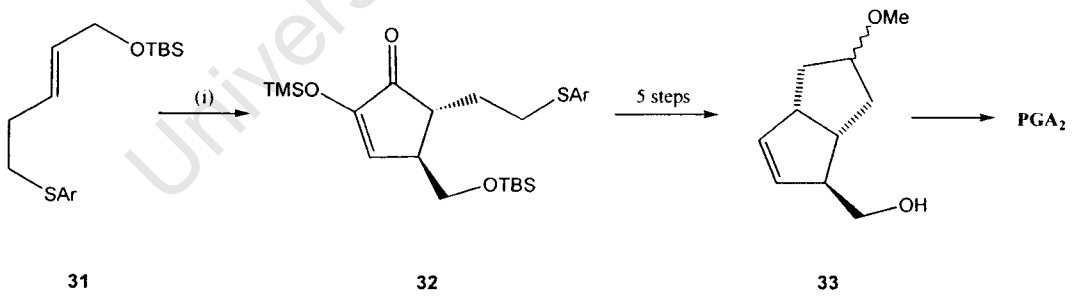
Scheme 1.4 *Reagents and conditions*: (i) H_2O_2, OH^-, rt, 100%, (ii) RZnBr, rt, 90%, (iii) $LiAlH_4$, rt, 3 days, 77%, (iv) FVT, 500°C, 10^{-2} mbar, 72%, (v) PCC, DCM, 91%, (vi) H_2, Lindlar cat, toluene.

The use of the so-called Corey lactone or derivatives thereof has also been widely employed in the synthesis of cyclopentenone PG's. This can be exemplified in the synthesis of PGA_2. Hodgson and Gibbs[25] generated the diol **(28)** by stereoselective rearrangement of the epoxide **(27)** with an optically active base. The diol **(28)** is converted in 3 steps to **29** which is transformed to the key PG intermediate **(30)** in two steps. This intermediate was used by Grieco and Corey in the synthesis of PGA_2 (Scheme 1.5). [26]



Scheme 1.5 *Reagents and conditions* (i) chiral base, benzene/THF, 0°C, 57%.

In an alternative PG synthesis, the sulfide-directing Pauson-Khand cycloaddition of 1, 2 disubstituted alkenes, was used by Corey for the synthesis of PGA_2 (Scheme 1.6). The key intermediate for the synthesis was the acetal **(33)**. It was generated in 5 steps from the *trans*-4,5-disubstituted cyclopentenone **(32)**. [27]



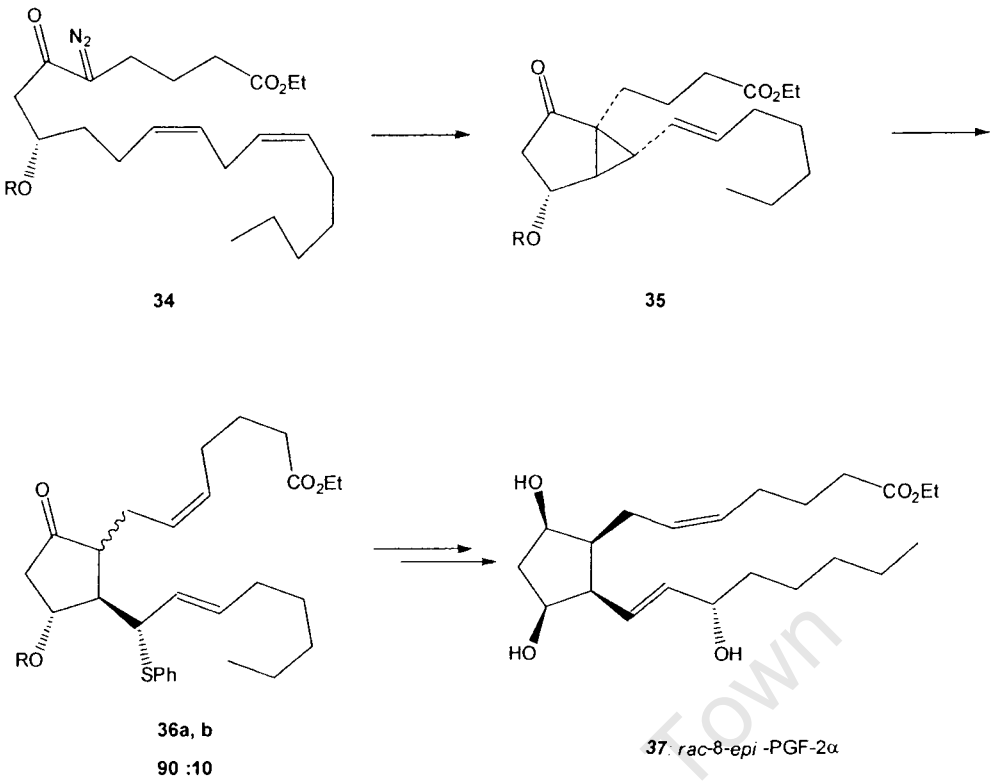
Scheme 1.6 *Reagents and conditions*: (i) [(trimethylsilyl)acetylene]hexacarbonyldicobalt complex, $PhCH_3$, 95°C, 30 h, 79%.

1.3. Synthesis of Isoprostanes

Synthetic routes towards both prostanes and isoprostanes are largely based on three strategies, the Corey synthesis, the two-component coupling and three-component coupling; although a number of other approaches have been adapted.

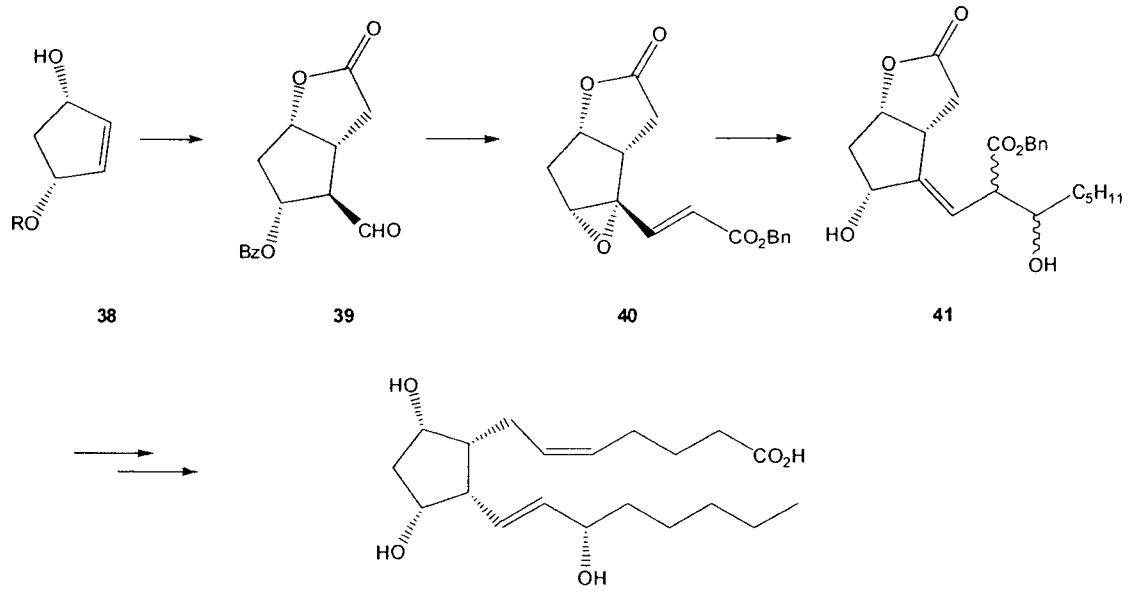
Much work has been done on the synthesis of isoprostanes of the F-series. Corey *et al* have described a biomimetic route to 8-*epi*-$PGF_{2\alpha}$ from arachidonic acid.[28] Mulzer *et al* have demonstrated the utility of a stereocontrolled biomimetic free radical 8, 12 cyclization in the synthesis of *ent*-12-*epi*-$PGF_{2\alpha}$.[29] Rokach *et al* had prior to this demonstrated using this methodology to generate the all *cis*-Corey lactone.[30,31] The Corey lactone has also been transformed to12-*epi*-$PGF_{2\alpha}$.[32] Larock *et al* have a used a Pd promoted intermolecular coupling of three different alkenes to generate 12-*epi*-$PGF_{2\alpha}$.[33]

Taber *et al* [34] have developed a novel strategy towards the synthesis of racemic 8-*epi*-$PGF_{2\alpha}$ ethyl ester (Scheme 1.7). Cyclisation of **34** with rhodium (II) octanoate proceeds to give the bicyclic ketone **(35)** with 77:23 selectivity for the *cis*-2, 3 arrangement. Boron trifluoride etherate-mediated addition of thiophenol to **35** under neutral low temperature conditions produces **36a** and **36b** with a diastereoselectivity ratio of 90:10 for **36a** to **36b**. The isoprostane **(37)** was revealed after a few functional group interconversions,



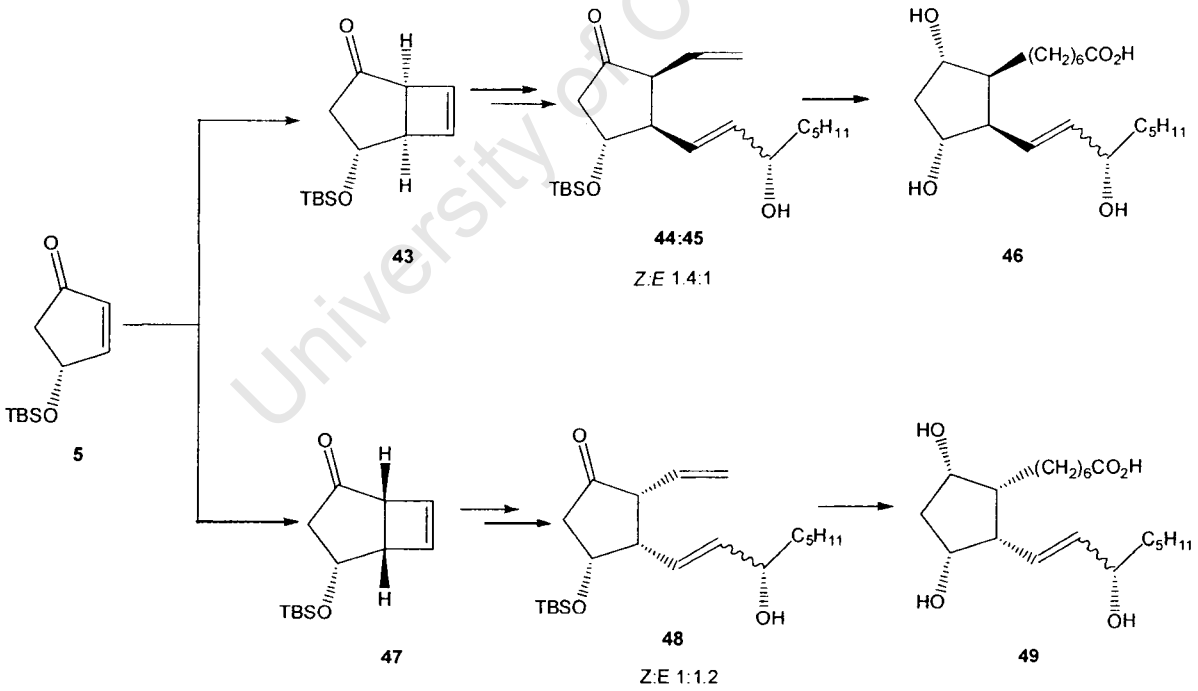
Scheme 1.7

Cha *et al* have synthesized 12-*epi*-$PGF_{2\alpha}$ and its C-15 epimer.[32] Their strategy involves the use of the Corey lactone **39**. Key to their approach is the SmI_2 induced reductive ring opening of the epoxy ester **40**. The resulting dienolate is trapped with an aldehyde for construction of the lower side chain. The requisite *cis*-dialkyl stereochemistry is established by stereocontrolled hydrogenation occurring at the less hindered convex face of the bicyclic lactone **41**. The upper side chain is then installed *via* Wittig olefination. A few functional group manipulations furnished the isoprostane 12-*epi*-$PGF_{2\alpha}$ **(42)** and its epimer at C-15 (Scheme 1.8).



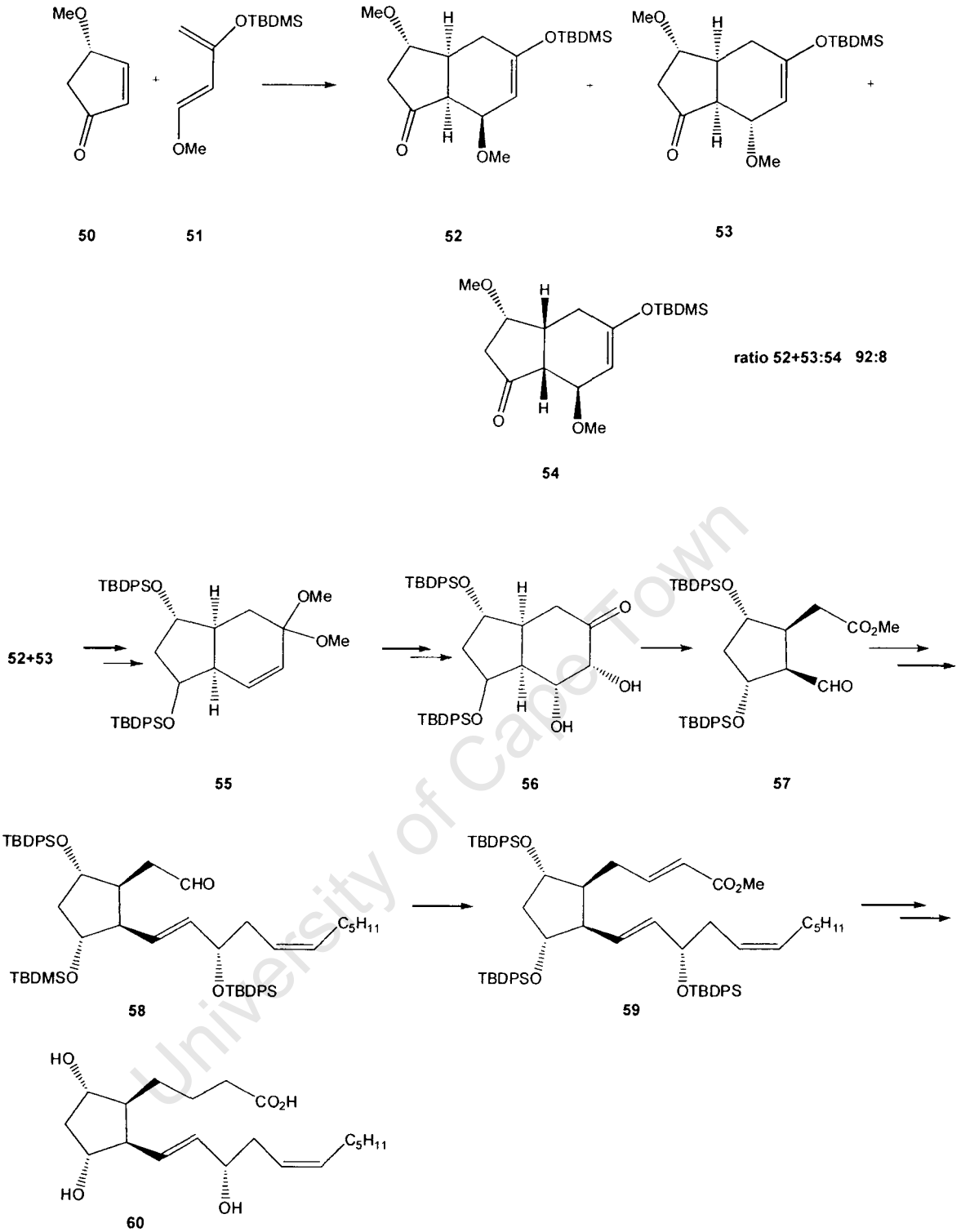
Scheme 1.8

Snapper *et al*[36] utilized a ring opening metathesis approach as the key transformation in the stereodivergent synthesis of diastereomers of the 15-F_2-IsoPs **49** (Scheme 1.9).



Scheme 1.9 Stereodivergent synthesis of diastereomers of the 15-F_2-IsoPs **49**

In a total synthesis of 8-epi-$PGF_{2\alpha}$ **60**, Rokach and co-workers[37] have selected a synthetic design based on a Diels-Alder approach as a means of generating the *cis*-relationship between the sidechains (Scheme 1.10). Key to this approach was control of the facial selectivity of the diene. This involved compelling the diene to approach from the less hindered face of the dienophile so as to obtain the two hydroxyl groups on the ring a to the plane of the ring and the sidechains *cis* to one another and anti to the hydroxyl groups. To achieve this, the hydroxyl group of the proposed diene was protected as a TBDPS group in a bid to encouraging facial discrimination by the diene. The Diels-Alder reaction produced a mixture of products **52** - **54** with a 92:8 ratio of product resulting from attack of the diene from the less hindered side to product resulting from attack on the more hindered side of the dienophile. The relevant products **52** and **53** were transformed to a gem methoxy derivative **55** *via* allylic rearrangement. This was converted in two steps to the *cis* diol **56**. Cleavage of the diol **56** with sodium periodate followed by treatment with diisopropylamine and methyl iodide afforded the methyl ester aldehyde **57**. At this point, the lower side chain was introduced using Wittig methodology followed by formation of the α aldehyde to give **58**. A two-carbon extension of the aldehyde introduced the upper sidechain affording **59**. Some functional group manipulation was then required to yield the isoprostane 8-epi-$PGF2_{\alpha}$ 60.

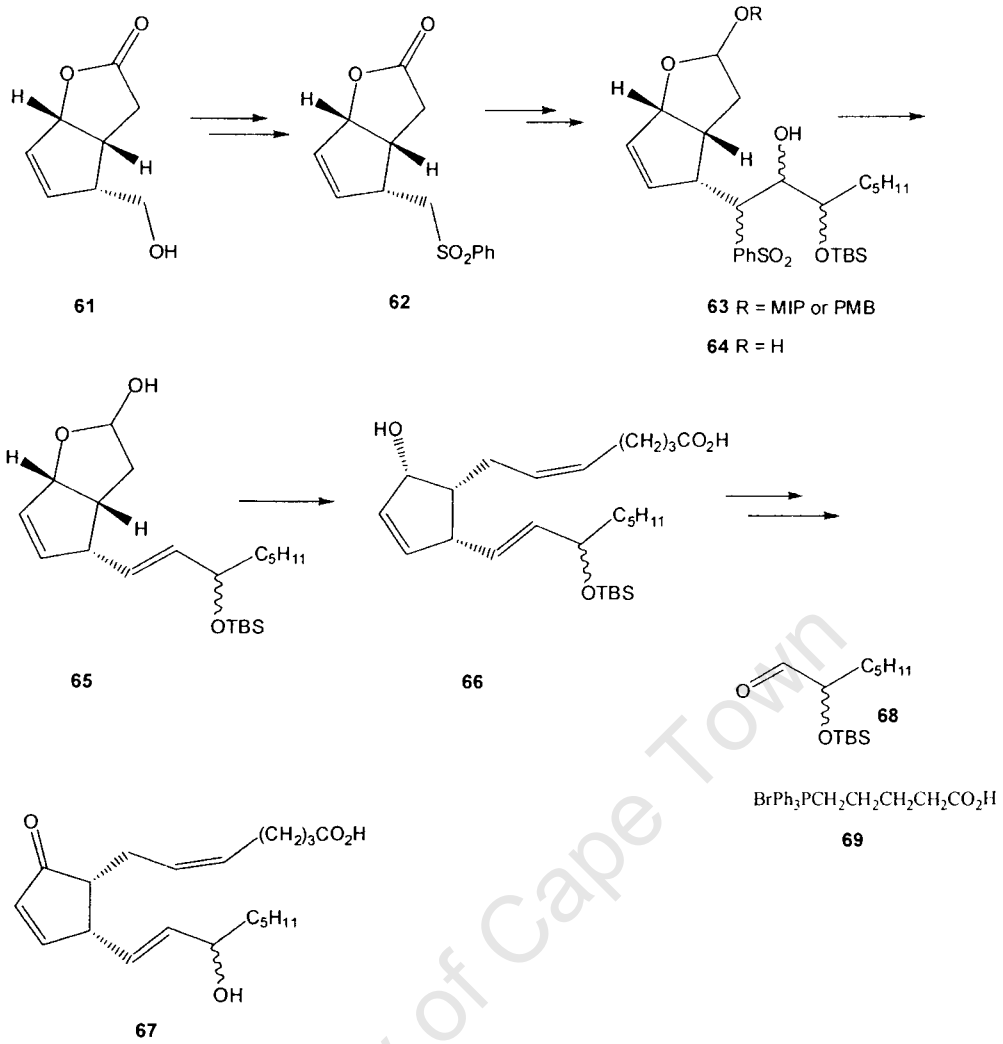


Scheme 1.10 Diels Alder methodology for the synthesis of 8-epi-PGF2$_\alpha$ **60**

While much work has been done on the synthesis of isoprostanes of the F-series, the cyclopentenone isoprostanes of the A and J series' have not been widely explored.

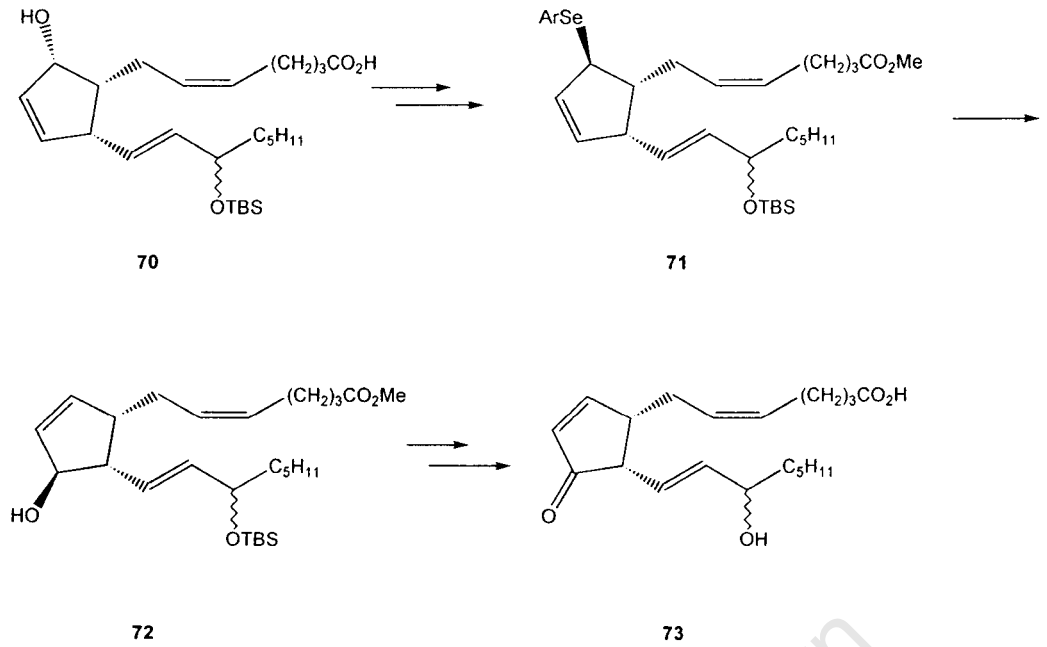
Vadari *et al*[38] have established a route towards the synthesis of the A_2- and J_2-cyclopentenone isoprostanes **(67)** and **(73)** respectively. Their approach utilizes two key steps for the formation of both the A_2- and J_2- isoprostanes. The first is the stereoselective assembly of the *cis*-disubstituted cyclopentene moiety **(66)**. The second critical point is the *E*-stereoselective Julia-Lythgoe olefination employed in the installation of the lower side chain (Scheme 1.11). The third key transformation, only for the formation of the J_2 isoprostane, involves 1, 3 allylic transposition of the C-9 hydroxyl group and oxidation to the ketone (Scheme 1.12).

In the first step, known lactone **(61)** is converted in two steps to the sulfone lactone **(62)** with maintenance of initial stereochemistry.[39] The lactone **(62)** was then protected as a MIP lactol to which the lower side chain **68** is added to yield **63**. This reaction utilizes the Julia-Lythgoe olefination and ensures preservation of the defined stereochemistry as well as *E* stereochemistry at the Δ^{13} double bond. Installation of the upper side chain exploits Wittig methodology with a non-stabilized Wittig reagent **(69)** and well known PG chemistry[40] to give the *Z*-olefin in the upper side chain. Oxidation followed by TBS deprotection yields the A_2 isoprostane **(67)**.



Scheme 1.11 Synthesis of *cis*-disubstituted cyclopentene **66** towards A_2 isoprostane **67** and J_2 isoprostane **73**.

The final key transformation in the formation of J_2 isoprostane is the 1, 3 allylic transposition of the C-9 hydroxyl group and oxidation to the ketone (Scheme 1.12). This is followed by functional group manipulation to afford the isoprostane **73**. The [2, 3] sigmatropic rearrangement of the secondary selenide **71** afforded the alcohol **72.** This was converted in three steps to the J_2 isoprostane **73**.



Scheme 1.12 Final transformation in the synthesis of J_2 isoprostane **73**.

1.4. Aims and Objectives

Given the biological activity of both the cyclopentenone prostaglandins and the isoprostanes, it has become necessary to find efficient synthetic routes to cyPG's with a view to evaluating their biological properties. The challenges involved in the synthetic pursuit of these molecules include the difficulty in installing the two sidechains with thermodynamically less favoured *cis*-dialkyl stereochemistry and as well as the propensity for epimerization of the labile stereogenic centres at C-8 and C-12 (PG numbering). Thus the synthesis of these molecules is not only challenging but also necessary as a means of obtaining sufficient material for biological studies.[8]

CHAPTER 2

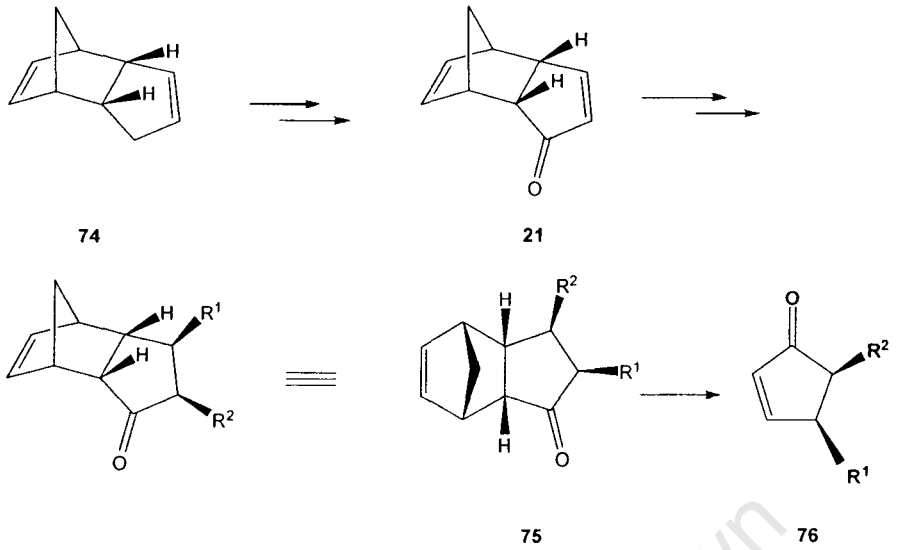
TWO AND THREE COMPONENT COUPLING APPROACHES

2.1 SYNTHETIC APPROACH

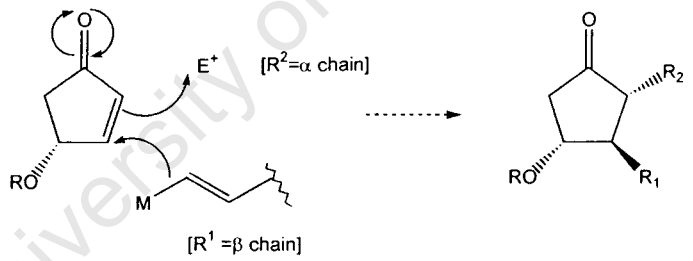
The synthesis of enantiopure cyPG's with the C_7- and C_8-sidechains orientated *cis* to each other presents a significant synthetic challenge considering the propensity of these compounds to undergo epimerisation, at the position α to the carbonyl group, in the presence of either acid or base

The envisaged synthetic approach encompasses the synthesis of the decadienone scaffold **(21)** in a 3-step sequence from dicyclopentadiene **(74)** (Scheme 2.1). This involves allylic oxidation of **(74)** to yield the acetate **(77)**. Hydrolysis of the acetate furnishes the corresponding alcohol **(78)** which is then oxidised to **21**. Installation of the first side chain takes place in a Michael sense followed by electrophilic trapping of the second side chain α to the ketone to give **75** (Scheme 2.1).

The obligatory orientation of the newly installed sidechains is determined by the architecture of the dienone **21** which dictates that addition occurs exclusively from the *exo*-face of the tricyclic system. This is reminiscent of the Noyori three-component coupling employed for the synthesis of prostaglandins (Scheme 2.2).[41,42] The second key step in the synthetic sequence involves a Lewis-acid mediated retro Diels-Alder reaction. This allows for the late-stage unveiling of the α, β–unsaturated system of the cyclopentenone PG **(76)** under mild conditions allowing for the preservation of the relative stereochemistry.



Scheme 2.1 Synthetic approach towards the synthesis of iPG's A-J.



Scheme 2.2 Three-component coupling approach.

2.2 SYNTHESIS OF THE STARTING DECADIENONE 21

Ogasawara and co-workers have illustrated the synthetic utility of **77** and **78** as precursors for the synthesis of **21** (Scheme 2.3). [43,44] Previous routes to **21**

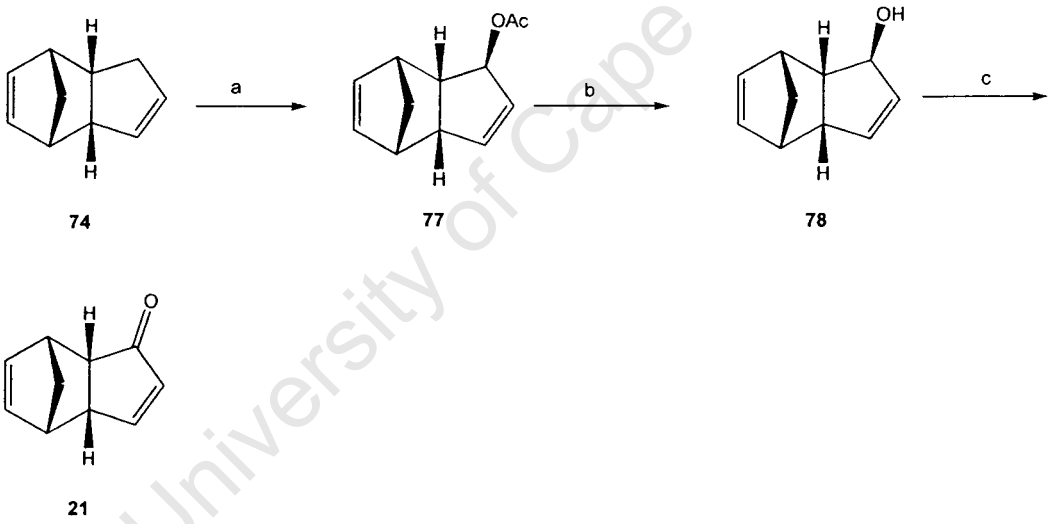
employed selenium dioxide oxidation of **74** to afford **78** hence rendering the oxygen functionality at the requisite position.[45,43] However, the toxicity of the oxidants led to exploration of alternative procedures by the authors. Preparation of the racemic acetate **(77)** involves the allylic oxidation of **74**. This was achieved through the use of manganese (III) acetate, prepared *in situ*, in the presence of warm acetic acid, acetic anhydride and catalytic potassium bromide. [43] The result afforded the acetate, in a stereospecific manner, with a yield of 50%. The yields obtained are comparable with those obtained for the selenium dioxide method which yields the *3-hydroxydicyclopentadiene* **(78)** in 57% yield.[46] The *exo* approach of the acetate group can be rationalized in terms of the sterically congested concave face **74**. Spectral data of **77** were identical to those reported by Takano and co-workers.[43] The diagnostic singlet for the methyl group of the acetate resonates at δ 2.02 in the ^{1}H NMR spectrum while the presence of the carbonyl moiety has been confirmed by the IR peak at 1720 cm^{-1}.

Hydrolysis of *exo-3-acetoxydicyclopentadiene* with K_2CO_3 in methanol for 18 h afforded the allylic alcohol **(78)**. Its ^{1}H NMR spectrum showed a new signal for H-3 at δ 4.07 which corresponds to the signal expected for a proton attached to a hydroxyl bearing carbon. The proposed structure is confirmed by the loss of the signal for the acetate methyl group in the ^{1}H NMR spectrum. The C-3 signal resonates at δ 79.2 in the ^{13}C NMR spectrum while the signal for the C=O carbon has disappeared. A broad IR absorption band at 3430 cm^{-1} supported the presence of hydroxyl functionality.

Oxidation of **78** to **21** was achieved using pyridinium chlorochromate adsorbed on alumina (PCC/alumina).[47] The reagent is prepared by adding alumina to a pyridinium chlorochromate (PCC) solution and removing the pyridine under reduced pressure. The reaction is performed by stirring excess oxidant with the alcohol **78** in a suitable solvent at room temperature. The use of alumina

reduces the reaction workup to simple filtration. The facile production of the reagent, the clean manner in which the reaction proceeds and simple isolation of the product makes this an attractive alternative for the effective oxidation of primary and secondary alcohols to aldehydes and ketones. The ^{13}C NMR provided evidence of the carbonyl carbon with a signal resonating at δ 210.6. This was confirmed by the carbonyl stretching frequency present at 1693 cm^{-1} in the IR spectrum.

The olefinic region of the ^{1}H NMR spectrum of **21** has four signals. Of these, H-4 and H-5 appear at δ 5.77 (doublet of doublets) and δ 7.36 (doublet of doublets) respectively. This marked difference in chemical shift is attributed to the conjugative electronic displacement of the α,β-unsaturated carbonyl substructure.



Scheme 2.3 *Reagents and conditions*: (a) $Mn(OAc)_3$, $KMnO_4$, KBr (cat.), AcOH, Ac_2O 70°C, 1 h, 50%; (b) K_2CO_3, MeOH, rt, 18 h, 85%; (c) PCC on alumina, hexane, rt, 18 h, 96%.

2.3 STRATEGIES FOR THE SYNTHESIS OF DISUBSTITUTED 3-OXODICYCLOPENTADIENE (21)

As illustrated (Figure 2.1), three alternative paths were explored to provide insight into the best synthetic method for elaborating **21** to yield the key intermediate **75**. Path A involves the stepwise installation of the first sidechain R^1, to generate the ketone **79**, followed by base-mediated installation of R^2 leading to **75**. The first step in Path B is the envisaged generation of the enol silyl ether **(80)** *via* conjugate nucleophilic addition followed by trapping of the enolate. The enolate is then liberated and electrophilic trapping by R^2 is expected to lead to **75**. A three component coupling (3CC) approach, first used by Nyori *et al* [48,42] was to be explored in Path C in the transformation of **21** to **75** *via* the metal enolate **81**. Common to the first step in all three of the proposed routes is the conjugate addition of the side chain, R^1.

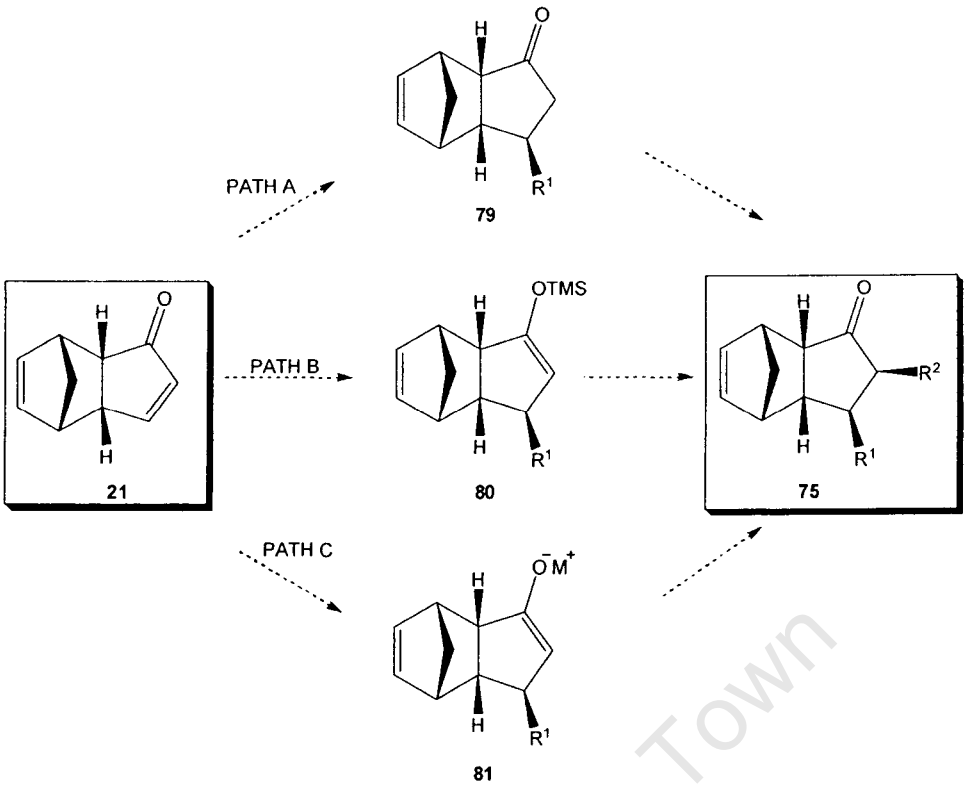


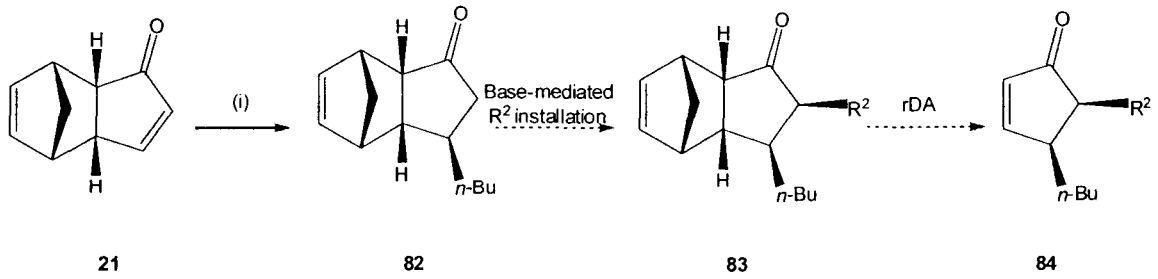
Figure 2.1 Routes towards the synthesis of **82**.

2.3.1 BASE MEDIATED APPROACH:

2.3.1.1 Conjugate addition of organocuprate Bu_2CuLi

Butyl ketone **(82)** was to be used as a model template in the synthesis of isoprostanes of PG's A-J **(84)** (Scheme 2.4). It was envisaged that the butyl R^1 chain could be used to develop the methodology as it provided an easily accessible form of the R^1 group. Furthermore, one of the aims of this programme is to investigate the use of an unfunctionalised chain in examining the effect of the prostaglandin R^1 group on the biological activity in these compounds

From this investigation, we hoped to gain insight into the preferred synthetic methods for the synthesis of these compounds.



21 82 83 84

Scheme 2.4 *Reagents and conditions*: (i) *n*-BuLi, CuI, Et_2O, 0°C to rt, 2 h, 62%.

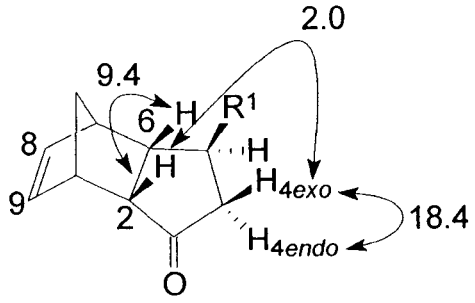
Organocuprate reagents are highly reactive and were expected to chemoselectively transfer ligands exclusively at the β-position of the enone **(21)** as well as stereospecifically to give the *exo* substituted tricyclodecanone. Carruthers[49] has illustrated that the factors that govern the stereochemical outcome of the addition of organocuprates to (poly)cyclic enones are not completely understood. It is accepted that approach of the reagent is in general perpendicular to the plane of the enone and is sensitive to both steric and stereoelectronic factors. Zwannenburg *et al*[50] have shown that in both 1, 2- and 1, 4-additions of organometallic compounds to **82**, addition invariably occurs from the convex face of the tricyclic skeleton. They propose that this is mainly as a result of the three dimensional structure of **21** and attribute this to the steric control exerted by the C8-C9 ethylene bridge. Hence, the compound **21** undergoes facile and stereoselective 1, 4-conjugate addition with the organocuprate.

Attractions between nucleophiles and electrophiles are governed by two related interactions.[51] The first is the electrostatic interaction between positive and negative charges and the second the orbital overlap between the HOMO of the

nucleophile and the LUMO of the electrophilic species. Both factors play a role but which factor dominates is dependent on the nature of the nucleophile and electrophile involved. Small, highly electronegative nucleophiles are subjected to electrostatic control while the reactions of larger nucleophiles are dominated by orbital overlap. These two types of reagents have been called hard and soft respectively. Hard nucleophiles have a higher charge density while the softer nucleophiles can be uncharged or have larger atoms with higher energy. Electrophiles can also be classified as hard or soft and in general hard nucleophiles prefer to react with hard electrophiles while soft necleophiles react with soft electrophiles. In the case of the carbonyl moiety, the carbon is considered to be hard due to the partial positive charge that resides on the carbon as a result of the polarization of the C=O bond. It will react with hard nucleophiles. In the case of an α, β-unsaturated carbonyl system, conjugation leads to stabilizing interaction and the π–bonds now react as a single, conjugated system as opposed to separate functional groups. This delocalization of the π–electrons in the conjugated system polarises the structure and renders the C=C bond electrophilic at the β-position. There are now potentially two positions of nucleophilic attack, one of which is hard and the other is soft. Here, the β-carbon does not have a high partial positive charge and is the site of the largest coefficient in the LUMO. Hence the β-carbon is a soft electrophile and is likely to react well with soft nucleophiles such as organocopper reagents in a 1, 4 addition manner.

The gross structure of **82** was deduced from its mass, IR and NMR data. The ^{13}C NMR spectra showed a diagnostic peak at δ 220.9 thus confirming the presence of the carbonyl moiety. Inspection of the ^{1}H NMR of **82**, a two bond geminal coupling of 18.4 Hz is observed between the H-4_{exo} and H-4_{endo} protons. This type of coupling is indicative of diastereotopic nature of these two protons and hence their magnetic non-equivalence. The assignment H-4_{exo} has been deduced from the long range four bond "W" coupling that it experiences

with H-2 (Figure 2.2). Mass spectroscopy further confirmed the presence of the proposed 1, 4-addition product.

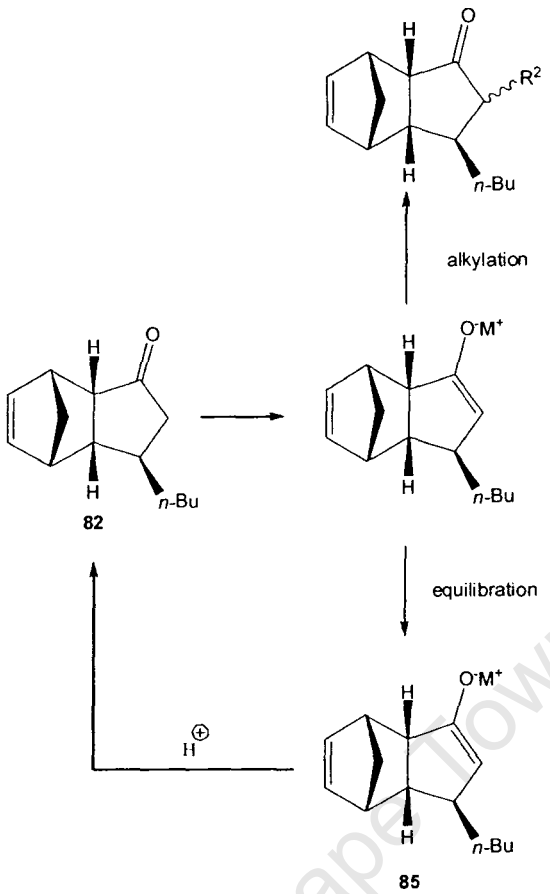


R1=*n*-Bu

Figure 2.2 Selected coupling constants for **82** (*J* values in Hz).

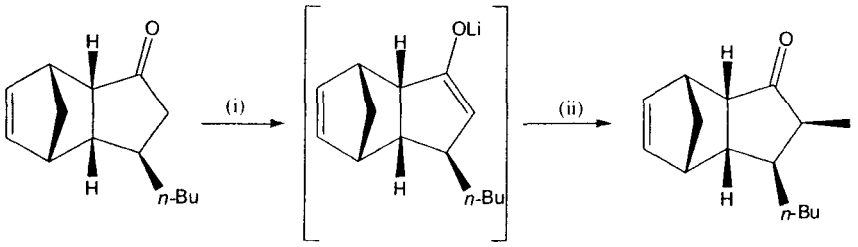
2.3.1.2 Alkylation with LDA as base:

With **82** in hand, we turned out attention to the installation of the α–sidechain. Following literature procedures,[52] our initial endeavours focused on the use of a kinetic base as a means of installing R^2. While the initial choice of the structural entity **21** was made in order to support *exo*-alkylation at positions 4 and 5 (Scheme 2.2), it was also expected that such a bridged system would suppress enolisation occurring at C-2. Under conditions of both thermodynamic and kinetic control, enolisation to C-2 is not expected to occur on the basis of statistical reasons. Furthermore, it is expected that the bridged system would suppress enolate equilibration which is the major obstacle in conjugate addition approaches to prostanoids. It is anticipated that if such equilibration does occur, it would be slow and protonation thereof would result in formation of the butyl ketone **(82)** (Scheme 2.5). Hence, regiospecific enolate generation is expected to occur from the corresponding ketone. Alkylation of the requisite regiospecific enolate affords the *cis*-dialkyl product.



Scheme 2.5

Johnson and Penning [52] have shown that reactive halides could be used in effecting this alkylation process. Hence, our studies focused on using the highly reactive iodides as the electrophiles in this substitution procedure. They along with others [53-54]have also demonstrated the importance of the presence of HMPA in these reactions. Suzuki *et al* have shown that the structure and reactivity of the lithium enolate of cyclopentenone are strongly influenced by co-existing co-solvent HMPA.[55]



82 86

Scheme 2.6 *Reagents and conditions*: (i) LDA, THF, -78°C (ii) Bu_3SnCl, HMPA, MeI, 62%.

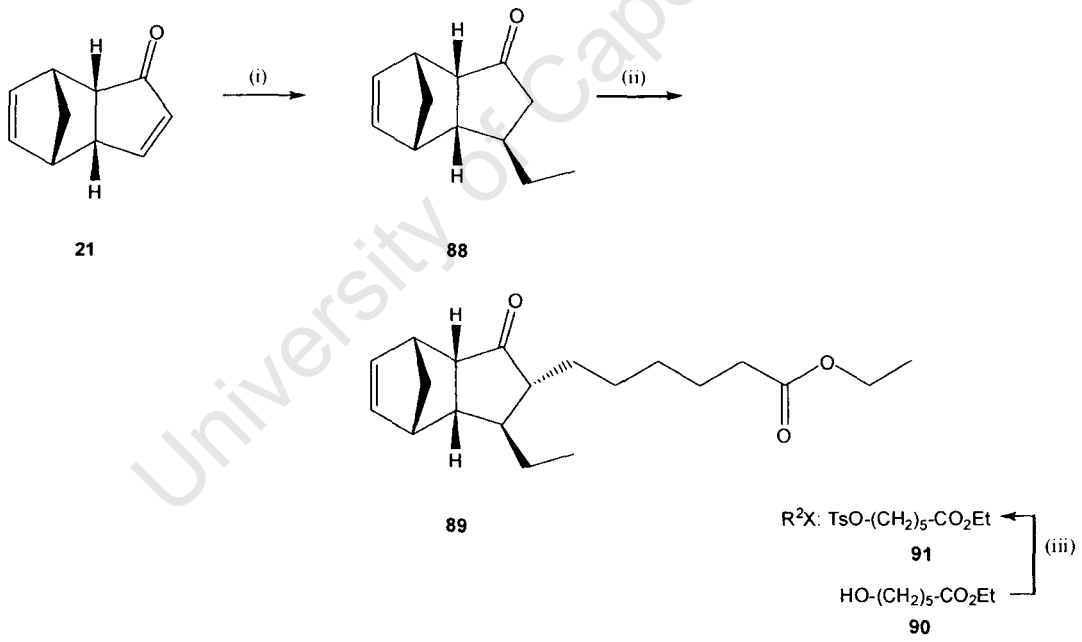
Initial alkylation studies were carried out using iodomethane. The required kinetic enolate was generated with LDA and Bu_3SnCl in THF and the enolate successfully alkylated with MeI. The tributylstannyl chloride was used to transmetalate the lithium enolate generated by enolisation of **82**, which has been reported to produce a slower yet cleaner reaction with fewer by-products.[52] Its ^1H NMR was used to verify the relative stereochemistry at positions 4 and 5 of **86**. H-4 in **86** appears at δ 2.19. This corresponds to the chemical shift for H-4_{endo} (δ 2.20) in **82**. Hence, one can deduce that addition occurred at the concave face of **82** to yield the *cis*-product. An alternative procedure to the same compound has been explored and will be discussed later (Scheme 2.14).

Having demonstrated that the two sidechains could be installed with control of regio- and stereoselectively, we sought to extend this methodology to different groups which could be manipulated to yield PG's A and J and analogues thereof. Despite the success achieved with the relatively sterically undemanding methyl-substrate, it was anticipated that larger substrates might provide a stiffer synthetic challenge. A number of different activated alkyl substituents were investigated for installation of R^2, the first being *5-(tetrahydro-2'-pyranyloxy)-1-iodo-pentane* **(87)**. With our substrate, this result proved elusive but to some extent the problem was overcome using conditions of thermodynamic control (Scheme 2.10). These findings are elucidated below.

Attempts with various other reactive sidechains proved unsuccessful which led to the exploration of alternative methods for constructing these molecules.

In pursuit of generating analogues of these structures, efforts were made to install a sidechain similar to that found in the PGA- and J-series', only one carbon atom shorter.

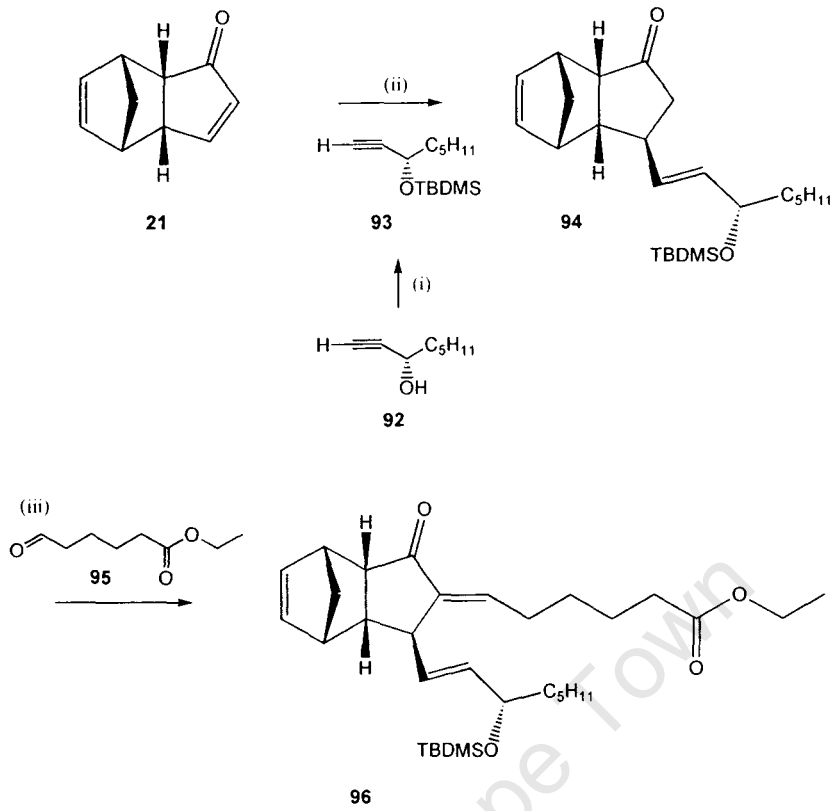
The reactive alkyl agent utilized was the tosylate **(91)** which was generated from ethyl 6 hydroxy-hexanoate **(90)** (Scheme 2.7). The reaction of **91** with the butyl ketone **(82)** proved unsuccessful. This led to an investigation into the effects of a shorter R^1-chain on the reaction. As such, the butyl-chain was substituted with an ethyl chain. The ethyl ketone **(88)** was synthesized using magnesium cuprate methodology to install the ethyl group in the β-position of **21** (Scheme 2.7).



Scheme 2.7 *Reagents and conditions*: (i) C_2H_5Br, Mg, CuI, Et_2O, 80% (ii) LDA, **91**, THF, 8% (iii) TsCl, Et_3N, CH_2Cl_2, 66%.

Analysis of the NMR data indicates formation of the *trans* rather than the required *cis*-product. This is supported by considering the chemical shifts of the H-4 protons in **88**. These have been shown to resonate at δ 1.89-1.96 (H-4_{exo}) and δ 2.20 (H-4_{endo}). The presence of H-4 at δ 1.54-1.80 as part of a 12 proton multiplet in the ^{1}H NMR spectrum of the addition product **89** indicates that the stereochemical outcome of this reaction is the *trans*-product as depicted. Repeating the reaction using a larger excess of base (2.5 equiv) improved the yield only slightly to 15%.

The base-mediated addition of *ethyl-6-oxohexanoate* **(95)** to **94** was investigated. The species containing the prostaglandin side chain in the β-position **94** was synthesized *via* a 1, 4 conjugate addition of **93** to **21** (Scheme 2.8). The enol silyl ether **(93)** is derived from the silylation of 1-octyn-3-ol. It has been demonstrated in the literature that this side chain can be inserted by use of the vinylstannane of **93**.[56,57] However, it is important to note that the preparation of *E*-vinylstannanes, formed *via* hydrostannylation of 1-alkynes is neither regio- nor stereospecific for generation of the *E*-isomer. Hydrozirconation of 1-alkynes using the Schwartz reagent provides a route towards stereo- and regiodefined *E*-isomer formation. The alkenylzirconate is transmetalated to give the cyanocuprate[58] (See Scheme 1.3). Thereafter conjugate addition of the cuprate to **21** inserts the β–chain to yield **94**. Treatment of **94** with LDA generated the enolate which was quenched by the aldehyde **95** to give **96** with the expected *exo*cyclic olefinic bond in only 4% yield (Scheme 2.8). The reaction yielded a number of by-products at first assumed to be diastereomeric β-hydroxy ketones. Attempts, however, to encourage these to form the α,β-unsaturated ketone failed. Attempts at the three component coupling approach produced similar results (Scheme 2.27). The longer β-sidechain could account for the low yielding result. NMR evidence does however support the structural assignment.

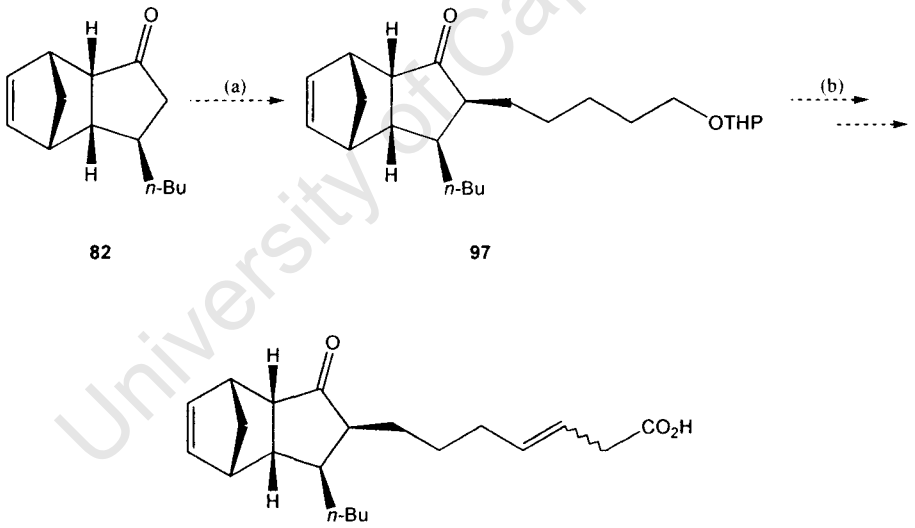


Scheme 2.8 *Reagents and conditions* : (i) TBDMSCl, imidazole, DMF, rt, 18 h, 78%, (ii) $Cp_2Zr(H)Cl$, **93,** MeLi, CuCN, THF, -50 to 0°C, 50%, (iii) LDA, **95**, THF, -78°C to rt, 4%.

While, it has been demonstrated that the ketone could be alkylated by sequential treatment with LDA and the halide or tosylate, the yields obtained for these reactions were low. Furthermore, the reactions are characterized by the production of a number of by-products which, at times, made product isolation difficult, if not impossible. Longer reactions times and increased temperatures contributed to the amount of by-product formed. The length of the alkyl chains seem to have a significant impact on whether the reaction proceeds at all but the complexity of the mixtures obtained and the poor yields resulted in the exploration of alternate methods for the synthesis of these compounds.

2.3.1.3 Alkylation using thermodynamic conditions:

In light of the difficulties in conversion, and low yields, obtained with the use of a kinetic base, we sought to explore the influence of the base on the reaction outcome. In particular, we wanted to determine if the use of the more reactive thermodynamic bases would allow for improved yields and less by-product formation. The envisaged synthetic pathway makes use of a base catalysed reaction that proceeds *via* a metal enolate transition state. *5-(Tetrahydro-2'-pyranyloxy)-1-iodo-pentane* **(87)** was to be utilized as the electrophile for trapping of the enolate to give **97** (step (a), Scheme 2.9). It was expected that preferential approach of the iodide would take place on the sterically less demanding *exo*-face of **82**. Step (b) would involve cleavage of the THP moiety, oxidation of the resulting primary hydroxyl group to an aldehyde followed by two-carbon Wittig homologation to reveal **98**.



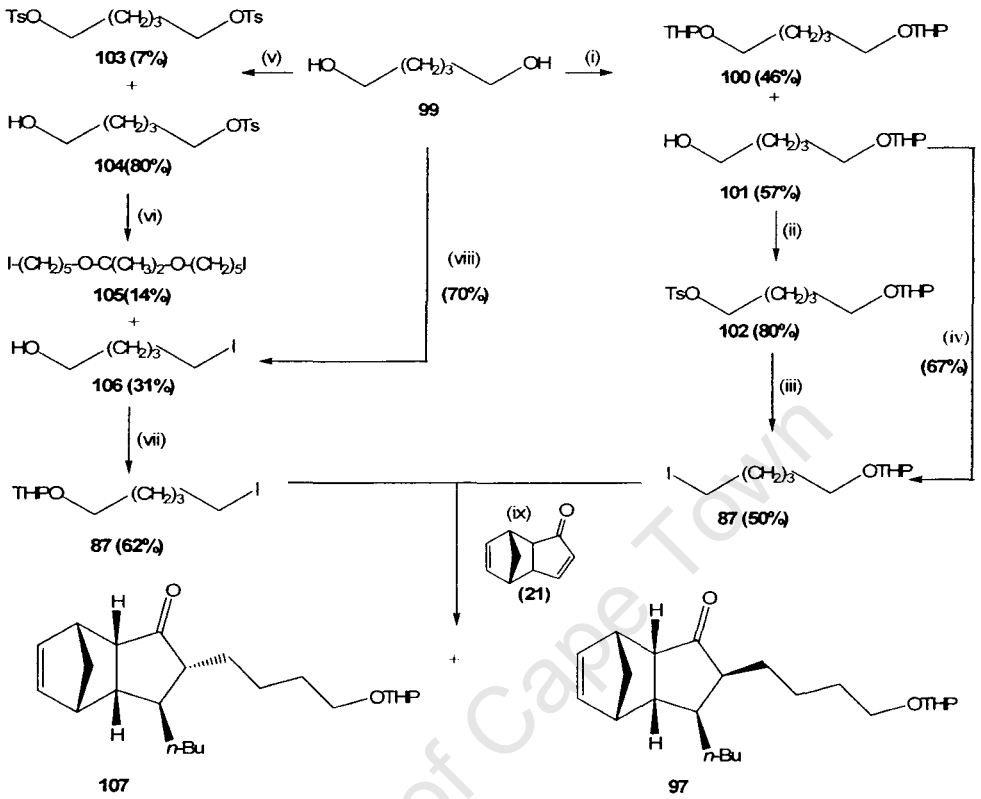
Scheme 2.9 Proposed synthetic route to **98**.

As illustrated (Scheme 2.10), the requisite alkylation agent for this reaction scheme was synthesized by a number of different routes in an effort to obtain the best yield. This optimized synthesis was necessary considering the large excess of the alkylation agent, typically 2-5 equivalents, required in the substitution reaction. Taylor, in a comprehensive review on organocopper conjugate addition-enolate trapping, notes that such an excess is necessary as, in addition to the reagent required to react with the enolate, further reagent is needed to consume excess organometallic reagent, reactive ligands etc. Diorganic cuprates usually produce one equivalent of alkylcopper upon completion of conjugate addition, hence excess trapping reagent is required when such reagents are used.[59]

In the first route (Scheme 2.10, step (i)-(iv)), 1,5-pentanediol **(99)** is first converted to the THP ether **(101)** in 57% yield, with the *bis*-protected product **(100)** being formed as the minor product. The hydroxyl functionality of **101** is then converted to the tosylate **(102)**. The tosyate is then converted to the iodide **(87)** using NaI and acetone. The two step transformation from **101** to **87** can be performed in one step with the use of triphenylphosphine, iodine and imidazole.

The second route, encompassing steps (v)-(viii), begins with the same starting 1, 5- pentanediol **(99)** which is stirred in the presence of Ag_2O, TsCl and catalytic KI in dichloromethane to yield the tosylate **(104)**.[60] In this case, only 7% of the ditosylated product **(104)** is isolated. Stirring with sodium iodide and acetone led to the conversion of **104** to **106** in 31% yield. [61-63] A by-product of this reaction is the acetal **(105)**. This is formed from the reaction of the mono THP protected product with acetone and is a known by-product of the Finkelstein reaction.[62] The ^{1}H NMR demonstrates a C-2 symmetric product with a singlet at δ 2.04 illustrating the presence of the two CH_3 moieties adjacent to the oxygens of the acetal. These are clearly absent in **106**. THP-ether formation is the final step in forming the iodo-THP protected alkyl chain. The

yield for this route over 3 steps is only 15%. It is improved to 43% with direct conversion of 1, 5-pentanediol **(99)** to **106** with cerium trichloride heptahydrate and sodium iodide in acetonitrile.[64]



Scheme 2.10 *Reagents and conditions*: (i) TsOH, DHP, CH_2Cl_2, rt (ii) TsCl, Et_3N, CH_2Cl_2, 0°C to rt (iii) NaI, $(CH_3)_2CO$, reflux (iv) PPh_3, I_2, imidazole, Et_2O/CH_3CN, rt (v) Ag_2O, TsOH, KI, rt, (vi) NaI, $(CH_3)_2CO$, reflux, (vii) TsOH, DHP, CH_2Cl_2, rt (viii) $CeCl_3.7H_2O$, NaI, CH_3CN, reflux (ix) base as per table 2.1, THF.

Addition of the α-sidechain to **82** was attempted with the use of a number of different bases, utilizing conditions of both thermodynamic (Table 2.1) and kinetic control. In all cases, the reactions were characterized by low yields, with entries 2 and 3 yielding both the *cis*- and *trans*-addition products. As the conditions for thermodynamic control allow for slower reactions to occur and

the formation of the most stable products,[51] this could account for formation of the more thermodynamically stable *trans*-product. However, once formation of the *cis*-product has occurred, equilibration to the sterically demanding *trans*-product is expected to be slow as this requires the deprotonation of H-4_{endo}. It must, however be noted that while thermodynamic conditions afforded both *cis*- and *trans*-products, the yields obtained in these reactions were most promising for this set of reactions. Entry 1 illustrates the result obtained using potassium hydride as base. This reaction did not lead to complete conversion of the starting enone after 18 h with an excess of base. The most successful application utilized $KOBu^t$ (entry 2). A mixture of *cis*- and *trans*-addition products were isolated with an overall product yield of 62 %. A small amount of starting material (5%) remained unreacted. Similar results were obtained using only 0.8 equivalents of the base. Entry 3 makes use of the dimsyl anion as base. This is generated *in situ* by the reaction of NaH with DMSO.[65,66] This reaction yielded 30% of the required *cis*-product. Unreacted starting material accounted for the majority of the material recovered (40%).

Table 2.1 Thermodynamic bases investigated in the formation of **97** and **107**.

	Base	Equiv.	Solvent	Temp (°C)	Result	Ratio *(cis:trans)*
1	KH	1.5	THF	0°C	8% (*cis*) **97**	100:0
2	$KOBu^t$	1.1	DMSO	rt	27 %(*cis*) **97** and 35% (*trans*) **107**	1.3:1
3	$MeSO_2CH_2^-$*	1.2	DMSO	rt	5% (*trans*) **107** and 30% (*cis*) **97**	5.4:1

*Dimsyl anion generated from NaH in DMSO

Structure elucidation was accomplished with the help of spectroscopic (Table 2.2) and analytical evidence which confirmed the proposed structures of **97** and **107**. Through nOe experiments, it has been confirmed that **97** is the *cis*-product

and **107** is the *trans*-adduct. Irradiation of the signal assigned to H-4 (δ 1.93) of **107** shows an increase in intensity of the signals assigned to H-2 and H-6 as a result of through space relaxation. Since these protons are located on the *exo*-face of the molecule, it can be concluded that H-4 must be *exo* and **107** is the *trans* addition product. Having confirmed the structures and their relative stereochemistry by nOe, we sought to explain the observed differences in the chemical shifts of H-8 and H-9 by conformational analysis of **97** and **107**. In the *trans*-isomer **(107)**, the bulky C-4 alkyl group is arranged in the preferred pseudo-equatorial position. This results in a conformational change in the 5-membered ring resulting in the shift of the adjacent carbonyl group towards the C8-C9 bridge. H-9 therefore falls under the anisotropic effect of the carbonyl moiety which accounts for the observed downfield shift of H-9 in the *trans*-isomer. The *cis*-isomer **(97)** adopts a conformation which minimizes the eclipsing interactions between the alkyl groups on C-4 and C-5. This places the large C-4 alkyl group in a pseudo equatorial position which shifts the carbonyl moiety towards the C-10 bridge in this case. As a result, the anisotropic influence of the carbonyl group is removed. Thus a relative upfield shift for H-9 is observed in the *cis*-isomer. This interpretation has been confirmed by molecular modelling as illustrated in figure 2.3. Modelling confirmed a lower energy status of the *trans* isomer **107** with an energy difference of 2.54 kcal/mol (10.63 kJ/mol) between the two isomers.

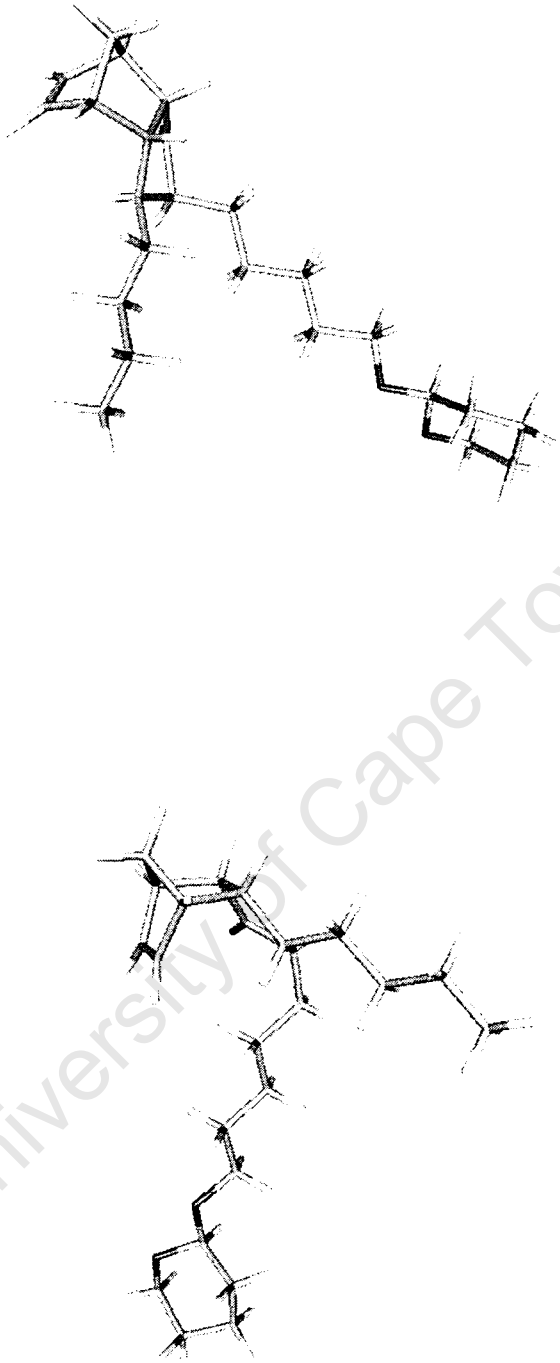


Figure 2.3 Conformations of **97** and **107** as determined by *ab initio* molecular dynamics calculations

The stereochemistry depicted for **97** and **107** was confirmed with NMR experiments. COSY spectra were used in the assignment of the diagnostic signals as evidenced in Table 2.2. Differences were observed in the chemical shifts of certain key signals of the two stereoisomers. There is a marked difference in the value of the chemical shift of the signals assigned to H-8 and H-9 in the *cis*-isomer **(97)** with H-8 appearing at δ 6.01 and H-9 at δ 5.96. By contrast, the corresponding signals in the *trans*-isomer **(107)** resonate at δ 6.02 and δ 6.13 respectively. Significantly, this constitutes an upfield shift of the H-9 signal by 0.17 ppm for the *trans*-isomer.

Table 2.2 Selected Data from the proton NMR spectra run in $CDCl_3$ of the stereoisomers **97** and **107**

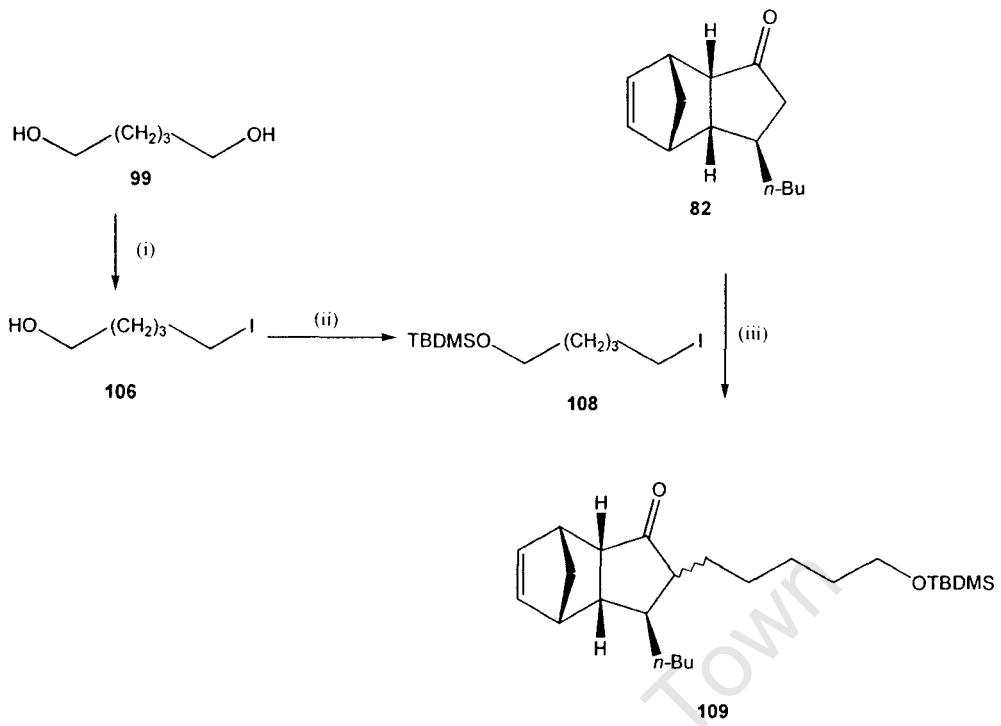
Proton	97 (*cis*)	107 (*trans*)
H-8	δ 6.01 (dd, *J* 5.7 and 3.0 Hz)	δ 6.02 (dd, *J* 5.8 and 3.0 Hz)
H-9	δ 5.96 (dd, *J* 5.7 and 3.2 Hz)	δ 6.13 (*J* 5.8 and 3.2 Hz)
H-1	δ 3.04-3.10 (m)	δ 3.12 (br m)
H-2	δ 2.87 (m)	δ 3.0 (m)
H-7	δ 2.87 (m)	δ 2.97 (br m)
H-6	δ 2.46 (m)	δ 2.54 (m)
H-2'	δ 4.58 (m)	δ 4.56 (m)
H-4	δ 1.81(m)	δ 1.93 (m)

The assignment of the relative stereochemistry was further confirmed by examination of the COSY spectrum of **107** which revealed a cross-peak between H-2 and H-4. This correlation is a consequence of 4 bond "W"

coupling which is only observed for the *cis*-isomer. Examination of molecular models reveals that in the *trans*-isomer H-2 and H-4 are ideally orientated thus allowing for long range coupling. By contrast, the *cis*-isomer **97** lacks the requisite "W" configuration and consequently no cross-peak between H-2 and H-4 is observed. While H-4 resonates as a multiplet in both the *cis*- and *trans*-isomers, the observed coupling in the COSY of **107** can only be attributed to "W" coupling which can only occur in the *cis*-isomer. This very diagnostic signal of H-4 is more deshielded in the *trans*-product (δ 1.93) relative to its position in the *cis*-product (δ 1.81). An increase in steric compression is known to lead to an upfield proton shift relative to its former position.[67,68] In the *cis*-addition product, H-4 is sterically more compressed, Hence, accounting for its upfield shift relative to the signal for the corresponding proton in the *trans*-addition product. The COSY spectrum of **107** was also able to indicate that H-4 does not couple to H-5 due to the dihedral angle between the two of 90°C in the *trans*-isomer. From inspection of molecular models, H-4 and H-5 should couple in **97** (dihedral angle =180°), although the large aliphatic quotient of the molecule makes it difficult to assign this proton absolutely.

In an attempt to investigate whether the protecting group of the α-sidechain affected the success of the reaction, **82** was treated under thermodynamic conditions with a base in the presence of a TBDMS protected five carbon iodide **(108)**. Treatment of **82** with $KOBu^t$ and alkylation of the resulting enolate of **82** with **108** rendered an inseparable mixture of *cis*- and *trans*-stereoisomers (Scheme 2.11). Based on an analysis of the integration for the signal for the H-8 and H-9 protons, it may be concluded that the *cis:trans* ratio is 2:3.

The reactive sidechain **108** was synthesized in two steps from 1, 5-pentanediol **(99)**. The diol was heated in refluxing acetonitrile in the presence of sodium iodide and cerium trichloride to yield the iodo-alcohol **(106)**. The hydroxyl group was protected as the TBDMS ether using TBDMSCl in the presence of triethylamine to afford **108**.

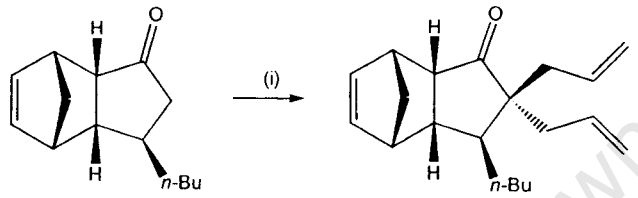


Scheme 2.11 *Reagents and conditions*: (i) $CeCl_3.7H_2O$, NaI, CH_3CN, reflux, rt, 70%, (ii) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 78% (iii) $KOBu^t$, **108**, DMSO, rt.

At this point, we considered the use of allyl bromide as the electrophile for installing the R^2 sidechain. Allyl bromide is readily available rendering it ideal considering the large excess of alkylating agent required to install the R^2 sidechain.

While competing *bis*-alkylation could be predicted with a large excess of base and allyl bromide, the compromise lay between driving the reaction to completion and the aforementioned *bis*-alkylation. To that end, attempts were made to alkylate **82** with allyl bromide and an excess of potassium hydride. This however yielded only the bis-allylated product **110** (Scheme 2.12). NMR evidence lay in the integration of the olefinic region. A ratio of 1:1 for H-8 or H-9:H-4[2] is expected for the single alkylation product. The presence of 8 olefinic protons in the ^1H NMR spectrum indicates the presence of two allyl

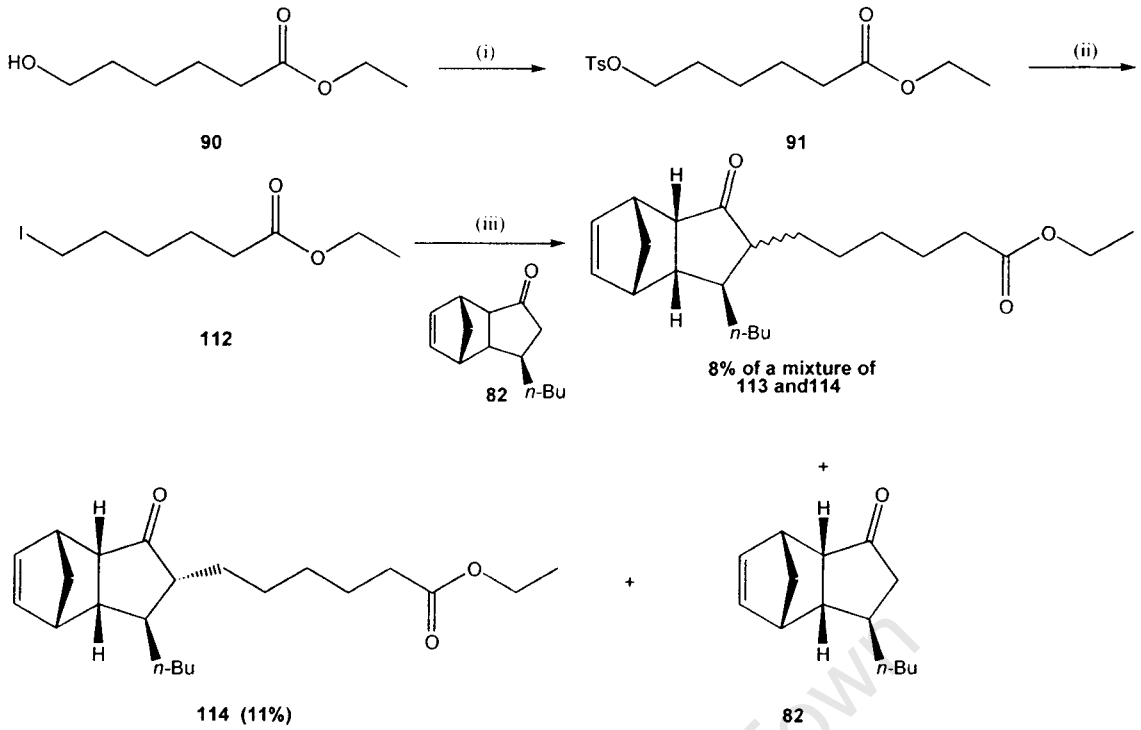
groups in the molecule. Attempts using potassium hydride as base rendered a separable mixture of the bisallyl product **110** as well as the mono-allyllated addition product **111**. NMR inspection of **111** revealed H-8 and H-9 at δ 6.13 and δ 6.18. At this point the relative stereochemistry was not defined. We were however also able to synthesize the mono-allyllated product using the triply convergent approach (Scheme 2.18) and at that point a full structural assignment was made (as described in section 2.4).



82 **110**

Scheme 2.12 *Reagents and conditions*: (i) KH, allyl bromide, THF, 38%.

Having demonstrated the applicability of $KOBu^t$ (Table 2.2) in generating the *cis*-addition products, its use was extended to the formation of potential analogues of PG's A-J as described above (Scheme 2.7). Alkylation of the enolate of **82** with **112** in the presence of $KOBu^t$ gave an inseparable mixture of the *cis*- and *trans*-stereoisomers **113 + 114** followed by the *trans*-product **114** which was isolated in only 11% yield (Scheme 2.13). The ratio of *cis:trans* in the mixture as determined by the NMR ratio is 1:1. The stereoisomers were assigned on the basis of evidence presented earlier wherein the signal for the H-9 proton experiences a marked downfield shift in the case of the *trans*-isomer relative to the corresponding signal in the *cis*-isomer. Assignment of the stereoisomers was confirmed at a later stage where the *trans*-isomer was unambiguously produced in a stereospecific manner (Scheme 2.24).



Scheme 2.13 *Reagents and conditions* : (i) TsCl, Et_3N, CH_2Cl_2, 0°C to rt, 66% (ii) NaI, $(CH_3)_2CO$, reflux, 83%, (iii) $KOBu^t$, DMSO, rt.

The alkylating agent **112** was synthesized in two steps from commercially available ethyl 6 hydroxy-hexanoate **(90)** (Scheme 2.13). Tosylation of the hydroxyl moiety was followed by iodination with NaI in acetone.

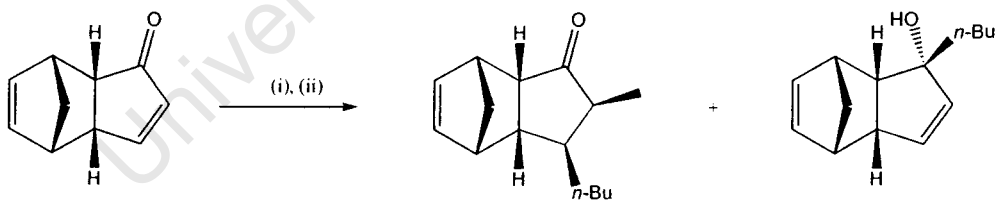
2.4 THREE COMPONENT COUPLING APPROACH

Potentially the most 'synthetically flexible and direct' route to prostaglandin molecules has been the triply convergent approach as pioneered by Noyori *et al.* There is a large body of literature on the investigations into the feasibility and refinements of this synthetic protocol over time. In this approach, the entire framework of the prostaglandin is assembled in a one pot sequence. This involves β–alkylation of the 4-oxygenated 2-cyclopentenone derivatives, this

process relying on the Michael-acceptor properties of the cyclopentenone nucleus. The β-chain is introduced with concomitant enolate generation *via* organometallic induced conjugate addition. The enolate can, in principle, be trapped with an electrophile to allow for regioselective α-alkylation (Scheme 2.2).

We sought to extend this methodology to our didecadienone system, employing the three component strategy with the hope of affecting *cis*-alkylation directed by the architecture of **21** (Scheme 2.1).

Chapdelaine and Hulce have reported that copper and lithium enolates were unreactive relative to those bearing other gegenions.[69] However, following the success reported by Johnson and Penning in a three component coupling (3CC) approach using MeI as electrophile on their substrate, we chose to repeat the reaction with our substrate **21** (Scheme 2.14). Thus we employed the 3CC strategy conditions elucidated by Johnson and Penning[52] As such, addition of dibutylcuprate to **21** followed by addition of HMPA and MeI at low temperature afforded the vicinally disubstituted **86** in 67% yield followed by the 1, 2-addition product **115** (30%) (Scheme 2.14).



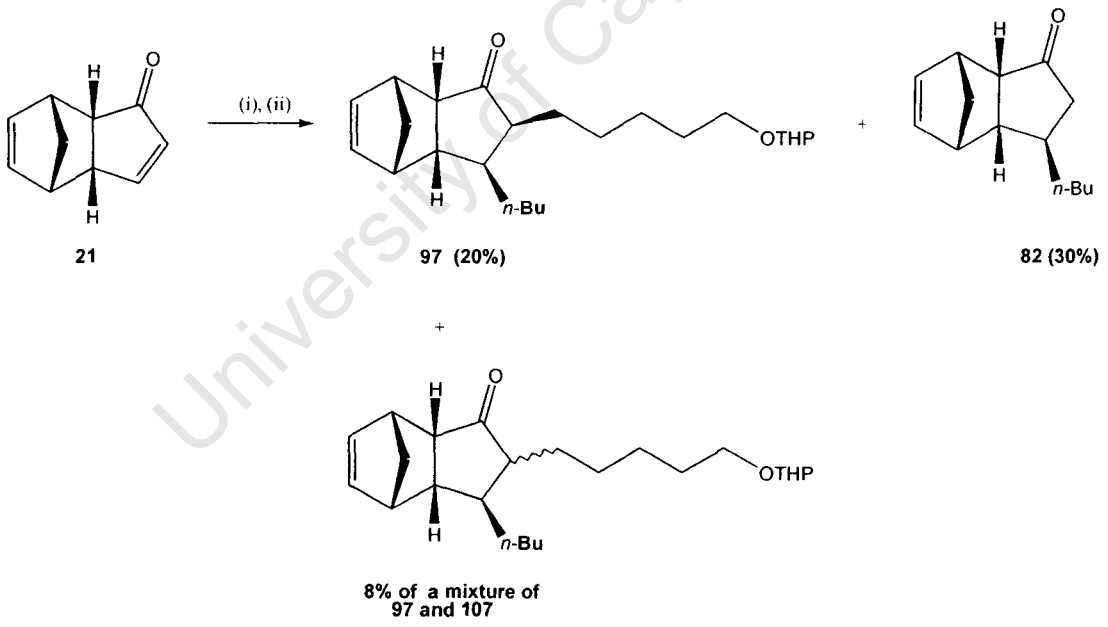
21 **86 (67%)** **115 (30%)**

Scheme 2.14 *Reagents and conditions*: (i) Bu_2CuLi, THF, -78°C, (ii) HMPA, MeI, -78° to rt.

NMR elucidation of **86** can be interpreted in a similar manner to that described earlier for this molecule (Scheme 2.6). The gross proposed structure of **115**

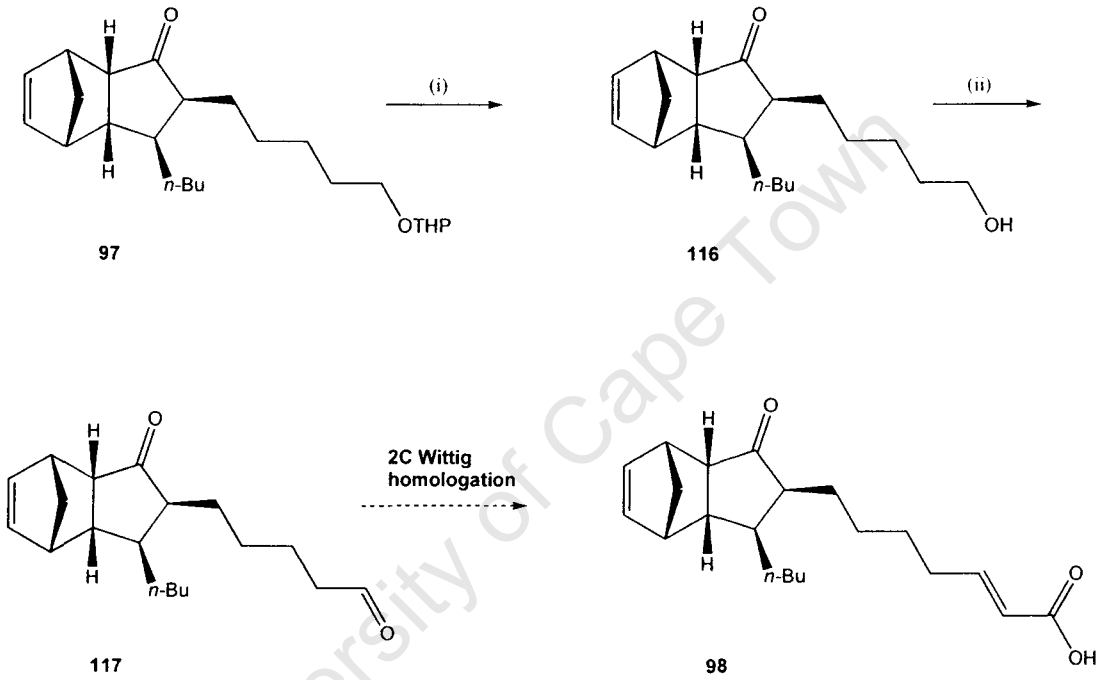
was verified by spectroscopic and analytical data. The presence of four signals corresponding to the olefinic protons in the ^{1}H NMR, as well as the ^{13}C NMR, indicated that Michael addition did not take place. This is further supported by an absorption band characteristic of an OH which appears in the IR spectra. Given that cuprates, in general, do not undergo 1, 2 addition to α, β–unsaturated compounds, it is proposed that incomplete formation of the cuprate results in the formation of **115**. This can be overcome by using the conditions which were used in the formation of **82** and stirring the CuI and *n*-BuLi at 0°C for a longer period of time.

A comparison using **87** (Scheme 2.10) as a source of the alkylating agent seemed prudent at this point. Addition of the lithium dibutylcuprate to **21**, followed by HMPA and **87** afforded **97** (20%) and an inseparable mixture of **97** and **107** (8%) as well as unreacted **82** (30 %) (Scheme 2.15). Longer reactions times *i.e.* 4 days failed to improve the conversion.



Scheme 2.15 *Reagents and conditions*: (i) *n*-BuLi, CuI, THF, 0°C, (ii) HMPA, **87**, -78°-0°C, 6 h.

The *cis*-product **97** has been hydrolysed using catalytic *p*-toluene sulfonic acid in methanol to give the free hydroxyl moiety in **116** which was then oxidized to the aldehyde **(117)** under Dess Martin conditions.[70-71] While no further work was carried out on **117**, this nonetheless provides a point of departure for the synthesis of iPG analogues. Wittig homologation of **117** would afford an analogue of PG-A or -J which would allow for testing of the effect of the double bond position on biological activity (Scheme 2.16).



Scheme 2.16 *Reagents and conditions*: (i) TsOH, CH_3OH, rt to 45°C, 79% (ii) Dess Martin periodinane, CH_2Cl_2, rt, quant.

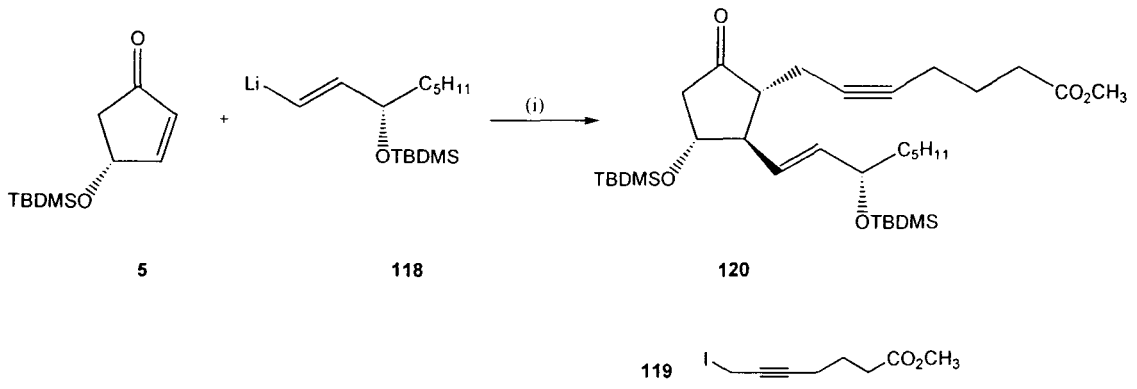
The structural assignments for **97** and **107** were made using ^1H and ^{13}C NMR spectra interpretation, similar to those described before for the assignment of **97** and **107** (Scheme 2.10). Relative stereochemistry was assigned on the basis of comparative R_f values to the already verified **97** and **107** as well as nOe studies. Conversion of **97** to **117** was confirmed by noting that aldehyde proton of **117** was shown to resonate at δ 9.74 as a singlet in its ^1H NMR

spectrum. The presence of a signal at δ 202.4 in the ^{13}C spectrum is further indication of the presence of the aldehyde carbon.

From these results, it emerges that the base-mediated approach using thermodynamic conditions provides us with a better recovered yield of the required *cis*-product. The drawback with all of these reactions, however, is that prolonged reaction times do not lead to complete conversion of the starting material but do lead to a larger observed decomposition and competing formation of the thermodynamically more stable *trans*-product. Furthermore, addition of excess base leads to *bis* α-alkylation (Scheme 2.11). From this it is clear that further work would involve a study looking at the effect of the base stoichiometry on the reaction outcome with a view to improving the yield.

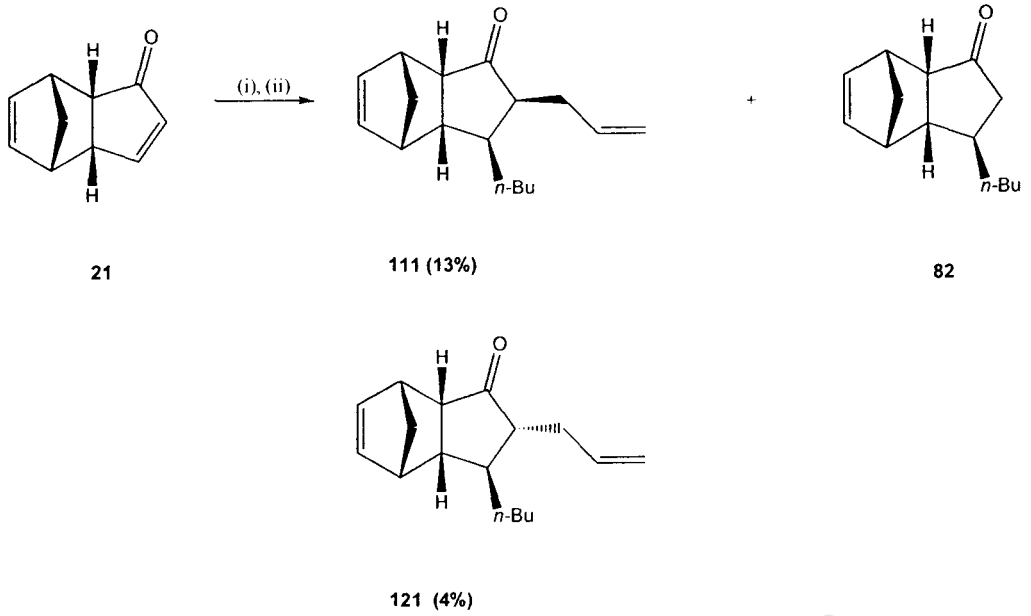
The reaction of lithium enolates with alkyl halides has been utilized widely for ketone alkylation although highly selective monoalkylation with strict exclusion of proton exchange has often remained difficult. Organozinc reagents have successfully been used as a transmetallation agents in the 3CC coupling protocol to overcome the difficulties encountered with the lithium and copper enolates. [23 72 58,73]

Suzuki *et al*[72] demonstrated that the reaction of equimolar amounts of the cyclopentenone species **(5)**, a vinyllithium β–side chain **(118)** and dimethylzinc followed by addition of the reactive α-sidechain **(119)** in excess would generate the triply coupled product **(120)** (Scheme 2.17).



Scheme 2.17 *Reagent and conditions*: (i) $ZnEt_2$, THF, **119**, -78°C, 71%.[72]

The applicability of this methodology to our system was investigated using allyl bromide as the source of reactive electrophile. Previous attempts to generate this product using base mediated methodology have proved unsuccessful (Scheme 2.12). The product of the reaction between *n*-BuLi and diethylzinc, generated *in situ*, was added to the enone **(21)**.[74,75] It is postulated that this reaction proceeds *via* a lithium methyl/butyl mixed zincate as the reactive species with only the sp^2 hybridized C-1 of **118** undergoing conjugate addition to the enone.[72] This is followed by addition of HMPA and allyl bromide. The resulting complex mixture, after separation, revealed 2 major products **111** and **121** accompanied by a large amount of unconverted butyl ketone **(82)** after several hours (Scheme 2.18).

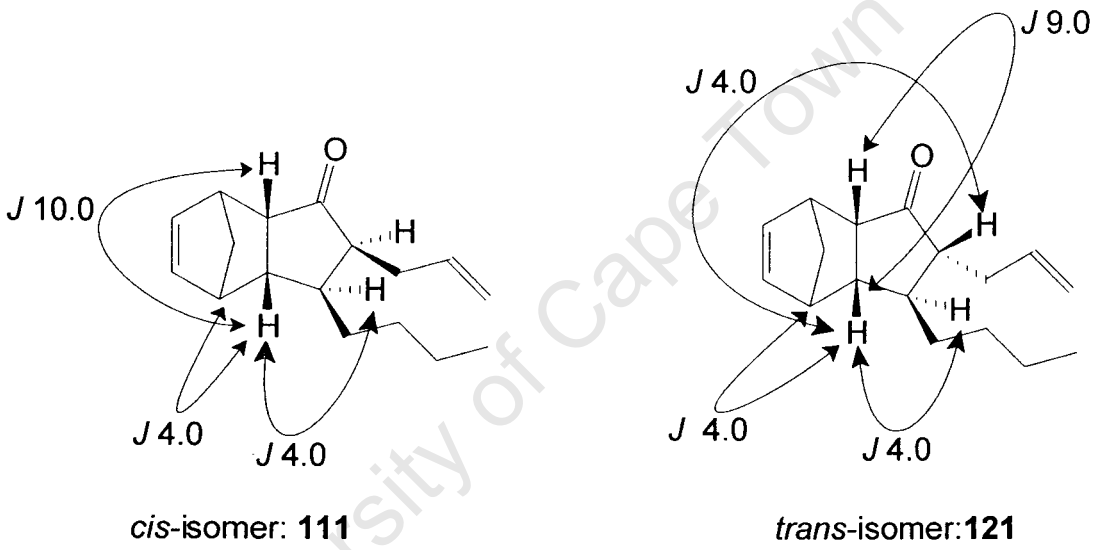


Scheme 2.18 *Reagents and conditions*: (i) n-BuLi, $Zn(CH_2CH_3)_2$, THF, -78°C (ii) HMPA allylbromide, THF, -40° to rt.

The ^{1}H NMR spectra of both **111** and **121** indicate the presence of the vicinally disubstituted moiety with no indication of *bis*-allylation occurring as seen before (**110**, Scheme 2.12). In contrast to the previous examples in which the chemical shift of H-9 was diagnostic in the assignment of the relative stereochemistry, in this case this was not possible. Consequently, alternate methods were used for stereochemical assignment.

The signal for H-4[2] resonates as a dddd in the range δ 5.66 -5.79 ppm in both isomers. H-4[3] is identified as a complex mulitiplet between δ 4.91-5.02. The signals that resonate at δ 2.56-2.60 and δ 2.58-2.65 ppm are assigned to H-6 in **111** and **121** respectively. These signals exhibit distinctly different coupling patterns and, by comparison, were invoked as a means of assigning the *cis*- and *trans*-isomers. H-6 in **111** is a much simpler signal than that of H-6 in **121**. Structure modelling indicates that only the *trans*-isomer would be set up for long range "W" coupling between H-6 and H-4. In both isomers, H-6 is capable

of coupling to H-2 with a large coupling constant and two smaller couplings to H-5 and H-7. Only, in the *trans*-isomer is there a predicted coupling between H-6 and H-4. This additional coupling reveals itself in the complexity of the signal for H-6 in **121**. The signal assigned to H-6 in **111** resonates as a ddd (*J* 10.0 and 2 x 4.0 Hz) while H-6 in resonates as a dddd (*J* 9.0 and 3 x 4.0 Hz) in **121**. Furthermore, structure modelling indicates that only the *trans*-isomer would be set up for long range "W" coupling between H-4 and H-5[2]. The weight of evidence allows us to conclude that **121** as the *trans*-isomer and **111** as the *cis*-isomer. The ratio of *cis:trans* is 3:1. The reaction does not proceed to completion and the butyl ketone **(82)** is isolated in 35% yield.



cis-isomer: **111** *trans*-isomer:**121**

Figure 2.3 Comparative couplings of H-6 of **111** and **121** (*J* values in Hz).

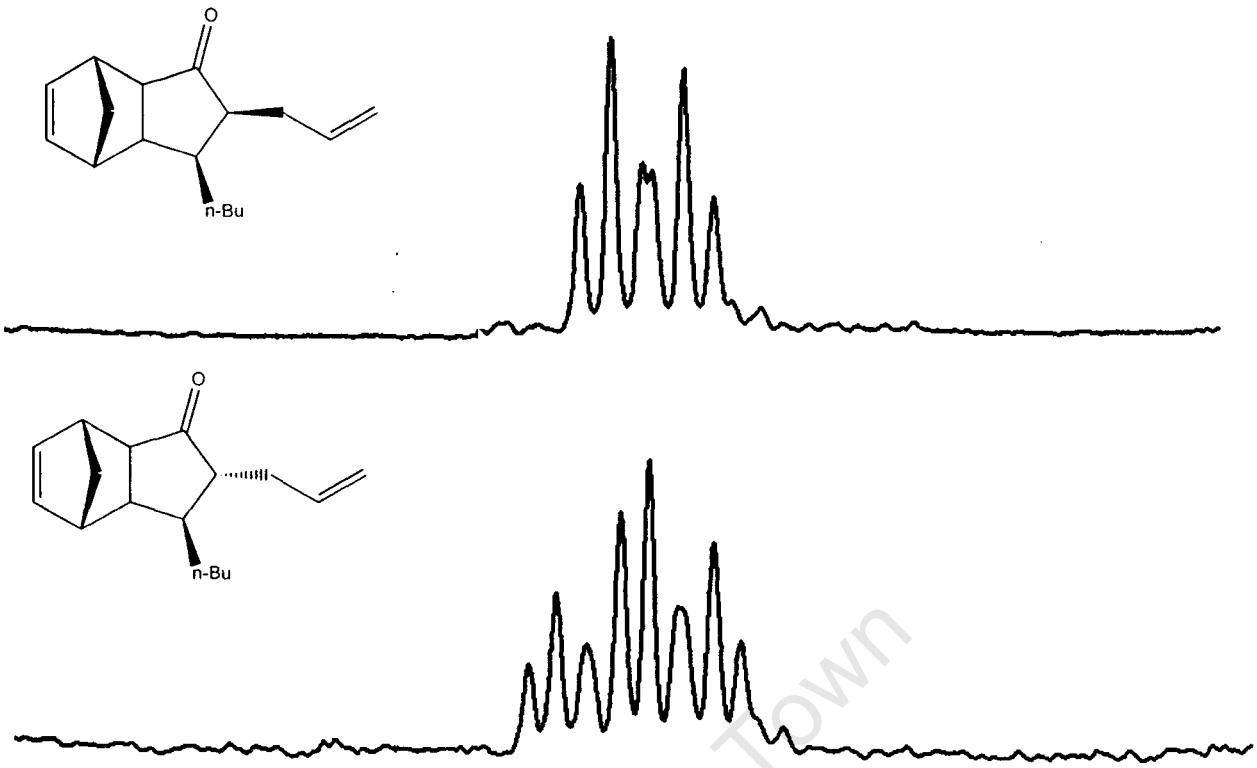


Figure 2.4 Comparison of signals for H-6 for **111** and **121**.

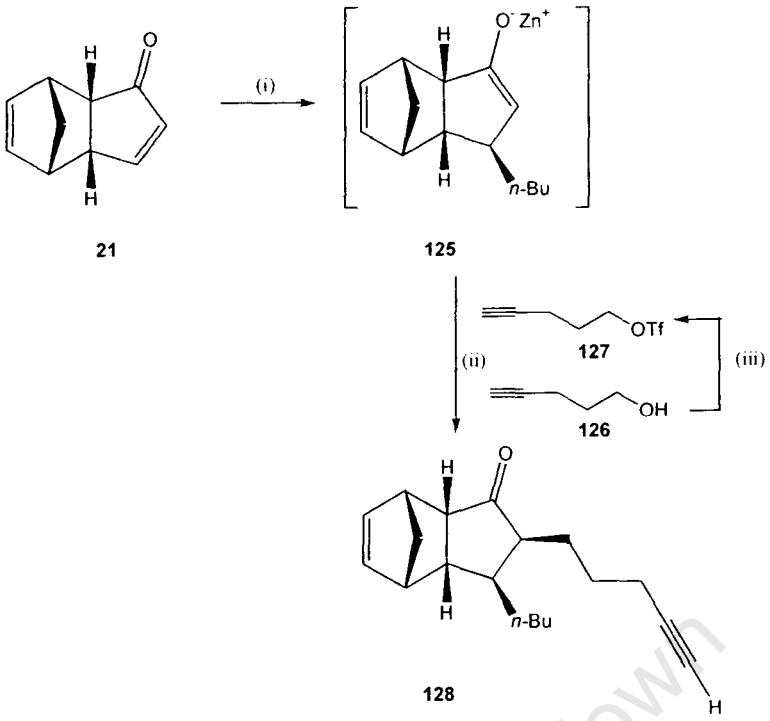
Further to our study on the influence of the leaving group on the success of the challenging α-alkylation, we sought to use triflates as the reactive electrophile species. Their use has been well documented [76,77] [78] and hence, it was clear that the use of triflates as a means of installing the α-sidechain needed to be investigated.

Trifluoromethanesulfonic esters are typically prepared from the reaction of an alcohol with triflic anhydride in the presence of a non-nucleophilic base at low temperature. As alkyl triflates are highly electrophilc, the use of pyridine as a base in their preparation is precluded as alkylation of pyridine occurs during

this reaction.* The use of a hindered base such as 2, 6-di-tert-butyl-4-methylpyridine (DTBP) is preferred in their preparation. The advantage associated with using this base is that it forms a precipitate which can be removed by filtration to render fairly pure triflate. After attempting the reaction using more readily available bases as illustrated in the literature,[76] we turned our attention to the use of this base in the synthesis of the alkyl triflates.

As indicated in the literature,[78] alkyl triflates are sensitive groups and not particularly stable. Hence triflate formation is conducted simultaneously as the enolate generation. This allows for both mixtures to be maintained at the appropriate temperature and under inert conditions before the enolate is treated with a solution of the triflate transferred using a cannula. [79] The enolate is generated by treatment of **21** with the trialkylzincate intermediate generated from *n*-BuLi and $ZnCl_2$.TMEDA.[75,74] This zincate undergoes conjugate addition to the Michael acceptor **21**. The use of a mixed zincate in 1, 4-addition reaction has been well illustrated by Watson and Kjonass.[80] The enolate thus formed is quenched with a large excess of the triflate to afford **128** (Scheme 2.19).

* There are examples which make use of pyridine in the literature.76. Decico, C.P., Grover, P. *J.Org Chem.* **1996**, 61, 3534

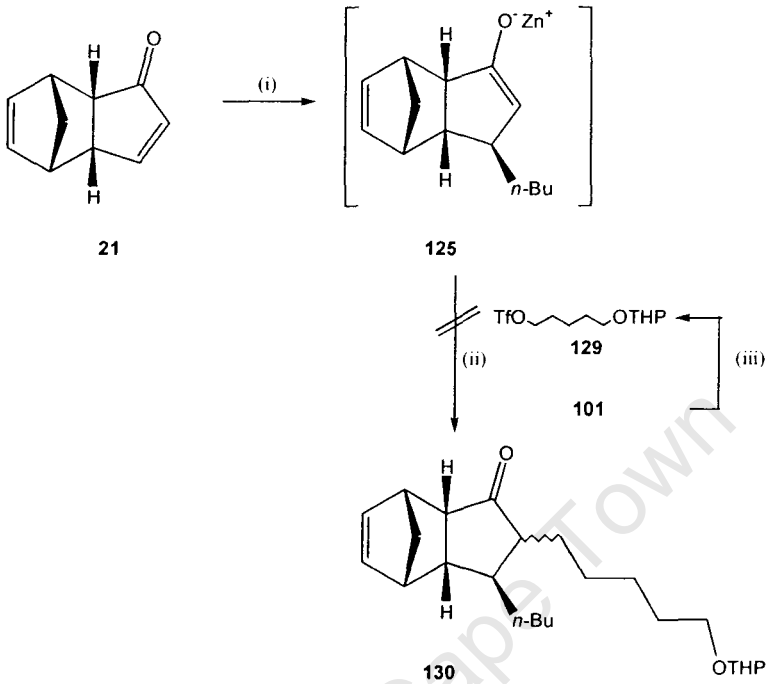


Scheme 2.19 *Reagent and conditions*: (i)n-BuLi, $ZnCl_2$.TMEDA, THF, -48°C to 0°C, (ii) HMPA, **127**, -78°C to -40°C, 18 h, (iii) Tf_2O, Et_3N, CH_2Cl_2, -25°C, 10 min.

The ^1H NMR of **128** indicates the presence of the alkynic proton H-4[5] (δ 3.98). It also indicates the presence of the butyl chain. nOe studies were conducted by irradiation at one of the olefinic protons, C-8 or C-9 at δ 6.09. This revealed an enhancement of the signals corresponding to H-4. Thus H-4 is spatially close to H-8 or H-9, indicative of *cis*-product formation. The reactions attempted were characterized by low yields and large degree of decomposition. Attempts to generate these products from the enol silyl ether derived from the butyl ketone **(82)** are described below (Scheme 2.29). In this reaction, Et_3N was used as the base in the triflate generation.[76] The above reaction was repeated using triethylamine and 2, 6 ditert-butylpyridine as base for generation of the triflate without any significant change in the outcome.

The coupling reaction was reproduced using the triflate generated from the alcohol **(101)**. The triflate was prepared using the non-nucleophilic hindered

base, DTBP, under similar conditions as described above. A number of attempted couplings were made, all resulting in isolation of varying amounts of butyl ketone as the sole identifiable product.

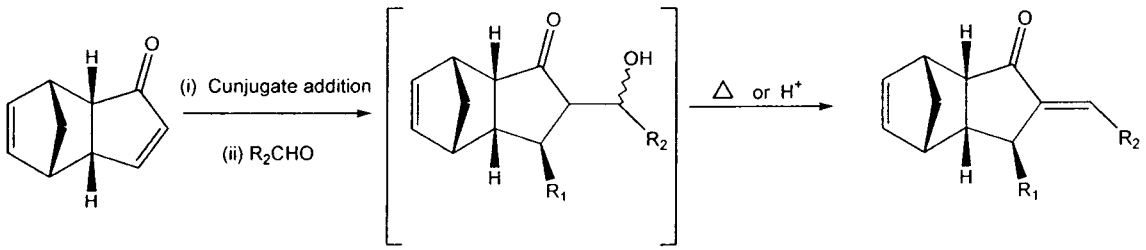


Scheme 2.20 *Reagent and conditions*: (i)n-BuLi, $ZnCl_2$.TMEDA, THF, -48°C to 0°C(ii) HMPA, **129**, -78°C to -40°C, 18 h (iii) Tf_2O, DTBP, CH_2Cl_2, -25°C, 3 h.

Coupled with the extremely cautious conditions required for generation of the triflate, this did not emerge as the most viable route for preparation of these compounds.

While the traditional 3CC strategies focused on the use of the so-called reactive alkylating agents such as iodides or triflates, we were also interested in exploring the use of aldehydes as coupling partners.[81-83] Eddolls and co-workers [82] have explored the use of three component coupling methodology using aldehydes to install the α-functionality. They were able to show that a one pot three component coupling procedure could be employed on both

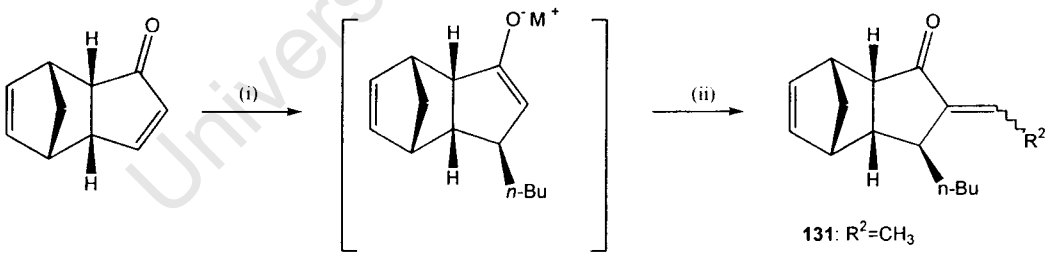
racemic and enantiopure substrates to give good yields of the *exo*cyclic enones (Scheme 2.21).



21

Scheme 2.21

Our extension of this methodology was in the use of the R^2 chains employed in the successive one pot alkylcuprate addition/aldol condensation/dehydration route. A few α sidechains were investigated (Table 2.3). The reagents used were Bu_2CuLi and Bu_2ZnLi (Scheme 2.22). Reagent addition was followed by aldehyde quench of the enolate intermediate **(131)**. From the result obtained, dehydration occurs in the absence of any significant heating or acid.



21 125

131: $R^2=CH_3$

132: $R^2=(CH_2)_4CH_3$

133: $R^2=(CH_2)_4CO_2Et$

Scheme 2.22 *Reagents and conditions:* (i) *n*-BuLi, CuI, $ZnCl_2$.TMEDA, Et_2O, -78°C (ii) R_2CHO, 0°C.

Table 2.3 Synthesis of exocyclic enones *via* one pot alykylcuprate addition/aldol condensation

Entry	Cuprate reagent	Aldehyde	Product) Yield, (%) (E/Z ratio)**
1	Bu_2CuLi	CH_3CHO	**131** (30) (100:0)
2	Bu_2CuLi	$CH_3(CH_2)_4CHO$	**132** (59)(100:0)
3	Bu_2ZnLi*	$CO_2Et(CH_2)_4CHO$	**133** (34) (100:0)

* was generated from $ZnCl_2$-TMEDA and *n*-BuLi in THF

** ratio determination-see page 61

Entry 1 uses the commercially available acetaldehyde as the α-addition moiety. NMR evidence in support of the product was unambiguous and pointed to the fact that the postulated *exo*cyclic olefinic group had indeed been installed. The presence of signal at δ 6.36 (qd, 3 x 7.5 and 2.1Hz) in the ^{1}H NMR indicated the presence of a new olefinic signal which could only be ascribed to H-4^1. The smaller coupling constant of 2.1 Hz is attributed to the allylic coupling between H-4^1 and H-5. A signal at δ 135.9 in the ^{13}C NMR spectra further verifies the presence of the olefinic moiety.

Entry 2 illustrates the result obtained with hexanal as the aldehyde. Once again, the *exo*cyclic olefinic proton, H-4^1, is identified as the most deshielded signal (δ 6.29, ddd, *J* 8.4, 7.2 and 2.4 Hz) with a small allylic coupling to H-5. The ^{13}C spectrum indicates the presence of three olefinic carbon signals resonating at δ 133.6, 135.9 and 137.2 with the latter being attributed to the newly generated C-4^1.

The third entry makes use of the aldehyde **95** generated *via* Swern oxidation of the readily available ethyl 6-hydroxy-hexanoate. The reaction is characterized by the production of a number of products. Included in these are presumably the four diastereomeric β-hydroxy ketones as well as the dehydrated form. Attempts to mesylate or tosylate the diastereomeric alcohols with a view to dehydrating these compounds were unsuccessful. The dehydrated product could however be isolated from the original reaction mixture in 34% yield.

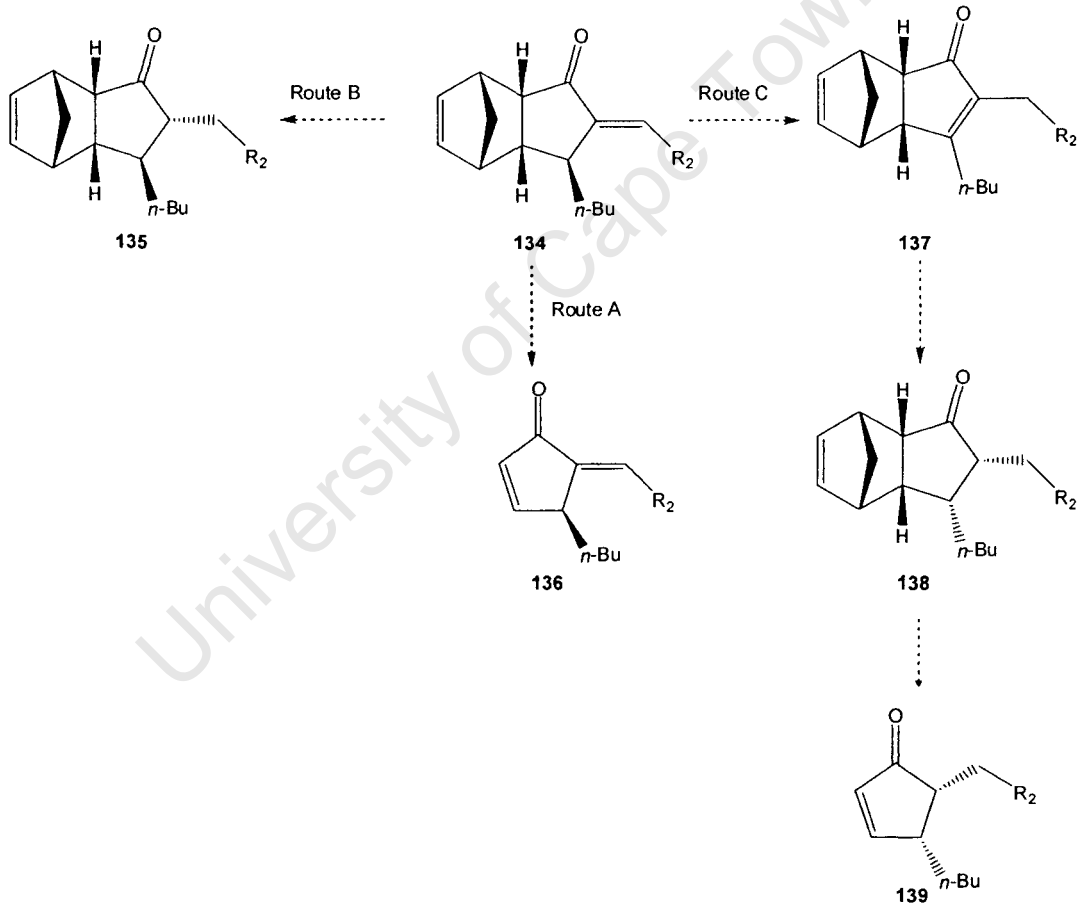
Enone **(133)** was shown by ^{1}H NMR to be a single diastereomer with a new olefinic resonance at δ 6.24 (ddd, *J* 8.8, 6.8 and 2.2 Hz) accounting for the presence of a new olefinic proton H-4^1. The small coupling constant can be attributed to allylic coupling with H-5 which may be singled out in the COSY spectrum as resonating at δ 2.39. A cross peak from H-5 highlights H-6 (δ 2.52) which is shown to couple to both H-2 and H-7. The protons H-1 and H-7 are located as cross peaks from H-8 and H-9 (δ 5.94, 2H, *J* 11.4, 5.6 and 2.6 Hz) .Therefore H-7 can be identified as resonating at δ 3.00 and H-2 at 2.96 (dd, *J* 8.9 and 5.0). The ^{13}C assignment is verified by cross referencing using HSQC experiments. This is also seen for **132** and **131**.

In this case, the alkyl moiety introduced in a 1, 4 addition sense was the trialkylzincate intermediate Bu_3ZnLi generated from the addition $ZnCl_2$.TMEDA to *n*-BuLi in THF and which may form an alkoxydialkylzincate.[84,85] Zinc enolates are thought to suppress the proton exchange between the enolate generated from the starting material and ketonic products. The $ZnCl_2$.TMEDA salt is a deliverable form of zinc and is more convenient to use than $ZnCl_2$ since it is non-hygroscopic.[86]

Table 2.4 Selected coupling constants for the enones the **131, 132** and **133**

	H-4^1	H-4^2	H-5
131	6.36 (qd, *J* 3 x 7.5 and 2.1 Hz)	1.72 (dd, *J* 7.5 and 1.2 Hz)	2.40 (m)
132	6.29 (ddd, *J* 8.4, 7.2 and 2.4 Hz)	2.01-2.12 (m)	2.50-2.54 (ddd, *J* 8.8, 4.0 and 1.6 Hz)
133	6.24 (ddd, *J* 8.8, 6.8 and 2.2 Hz)	2.02-2.14 (m)	2.39 (m)

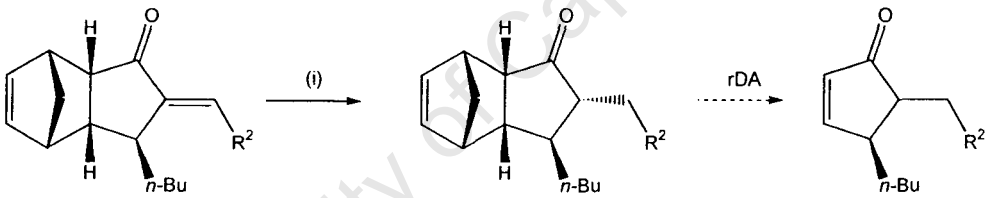
While the yields obtained for these reactions were not optimised, they were reproducible (Table 2.3). These *exo*cyclic enone species were seen as key intermediates for the production of a number of different types of prostaglandins *via* different routes (Scheme 2.23). Route A involves a rDA performed under Lewis-acid conditions to reveal the α, β-unsaturated cyclopentenone ring. This is a way into the formation of analogues of prostaglandins of this type. Route B involves a conjugate reduction with obligatory formation of the *trans* cyclopentenone prostaglandin. The initial step in route C, involves *exo*- to *endo*-cyclic isomerisation of the double bond. It is envisaged that at this point, reduction of this double bond would produce the analogue with the vicinal disubstitution being *cis*. A simple rDA would then give the cyclopentenone isoprostane.



Scheme 2.23

To this end, both **133** and **132** were subjected to conjugate reduction using the protocol developed by Stryker. (Scheme 2.23, Route B). Chemoselective conjugate reduction is effected with the use of the hexa-μ-hydrohexakis(triphenylphosphine) hexacopper complex in toluene.[87]

This bulky reagent will approach the *exo*-face of the substrate and hence it is anticipated that the relative stereochemistry of the α– and β–side groups would be *trans* (Scheme 2.24). This was verified *via* NMR experiments. Irradiation of H-4 (δ 1.94) during nOe experiments on **140** lead to the enhancement of the signals corresponding to H-2, H-7 and H-6. It can therefore be deduced that the relative stereochemistry is indeed *trans*. Similarly, irradiation of H-6 (δ 2.54) in **141** enhances the signal corresponding to H-4. The relative positions of H-8 and H-9 in **141** were verified using the COSY spectrum.

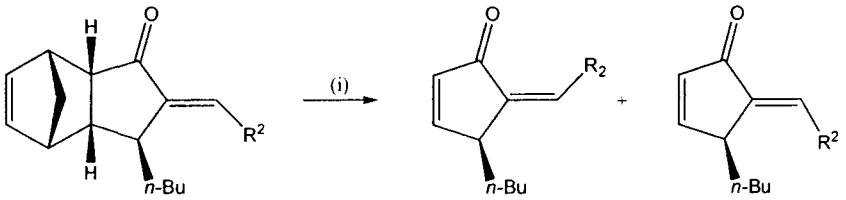


133: $R^2 = (CH_2)_4CO_2Et$ **140**:$R^2 = (CH_2)_4CO_2Et$ (42%)

132 : $R^2 = (CH_2)_4CH_3$ **141**: $R^2 = (CH_2)_4CH_3$ (63%)

Scheme 2.24 *Reagents and conditions*: (i) $[(Ph_3P)CuH]_6$, toluene, 18h.

In the elaboration of route A, **134**, was treated with ethylaluminium dichloride in the presence of maleic anhydride at 50°C. This affords two products which are identified as the *E*-and *Z*-adducts (Scheme 2.25).



133: R^2= $(CH_2)_4CO_2Et$ **142**:R^2= $(CH_2)_4CO_2Et$ (11%) **143**:R^2= $(CH_2)_4CO_2Et$ (80%)

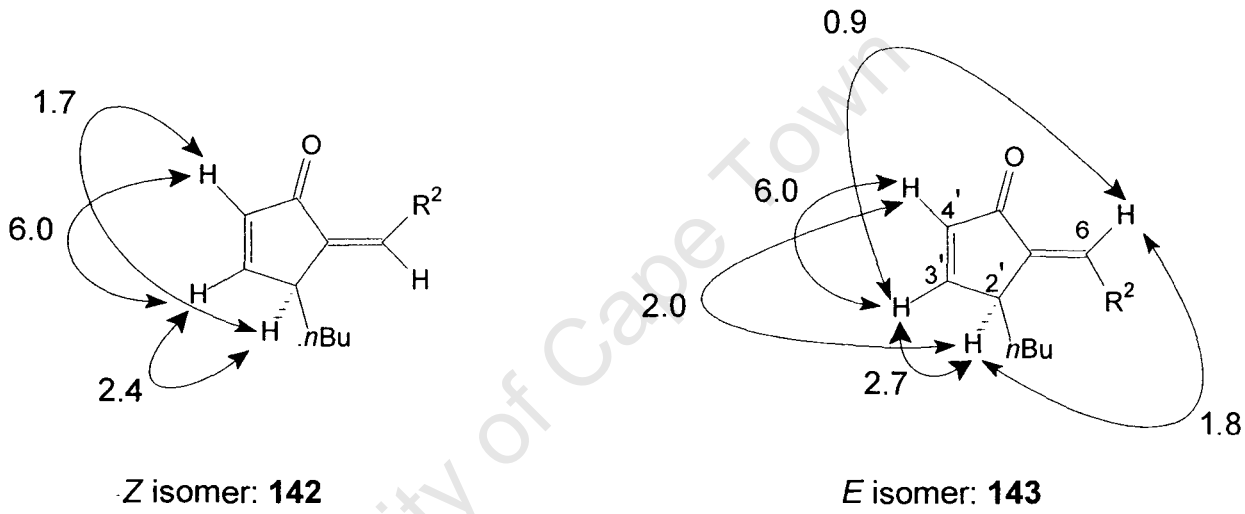
132: R^2= $(CH_2)_4CH_3$ **144**: R^2= $(CH_2)_4CH_3$ (11%) **145**:R^2= $(CH_2)_4CH_3$ (67%)

Scheme 2.25 *Reagents and conditions*: (i) $EtAlCl_2$, Et_2Cl_2, maleic anhydride, 50°C, 1.5 h.

Differentiation of *E*-and *Z*-products was assigned on the basis of NMR interpretation (Table 2.5). The olefinic proton, H-6, resonates at δ 6. 51 (tt, *J* 2 x 7.8 and 2 x 1.8 Hz) in the *E*-isomer **143** and at δ 6.01 (br t, *J* 2 x 7.6 Hz) in the *Z*-isomer **142**. The relative chemical shifts can be explained on the basis of the anisotropic effect of the carbonyl group. It is clear from the structure that the *E*-isomer is set up for H-6 to experience this effect and hence the downfield shift of H-6 in **143** relative to that of **142**. This signal can be regarded as a collapsed doublet of doublets in which H-6 of the *Z*-isomer **142** couples to the two H-5 protons. In the *E*-isomer H-6 resonates as a triplet of triplets coupling to both H-5 protons but also has a small allylic coupling to H-2′. This can be verified by a crosspeak from H-6 to H-2′ in the COSY spectrum. H-3′ resonates at δ 7.53 (ddd, *J* 6.0, 2.7 and 0.9 Hz) in **143** and δ 7.43 (dd, *J* 6.0 and 2.4 Hz) in **142**.The large coupling constant in both cases refers to that with H-4' while the intermediate in **143** and the smallest in **142** indicate the coupling to H-2′. The smallest coupling in **143** is the long range "*W*" coupling experienced with H-6. From model structures, only the *E* isomer is set up for such "*W*" coupling. A cross peak in the COSY spectrum from H-3′ to H-6 confirms this model structure elucidation. From this data **142** can be assigned as the *Z*-isomer and **143** as the *E*-isomer. The ratio of E/Z is 5:1.

Table 2.5 Selected chemical shifts and coupling constants for **142** and **143**

	H-4′	H-3′	H-2′	H-6
142(*Z*)	6.23 (dd, J 6.0 and 1.7 Hz)	7.43 (dd, *J* 6.0 and 2.4 Hz)	3.27(m)	6.01 (br t, *J* 2 x 7.6 Hz)
143(*E*)	6.32 (dd, *J* 6.0 and 2.0 Hz)	7.53 (ddd, *J* 6.0, 2.7 and 0.9 Hz)	3.48 (m)	6.51 (tt , *J* 2 x 7.8 and 2 x 1.8 Hz)



Z isomer: **142** *E* isomer: **143**

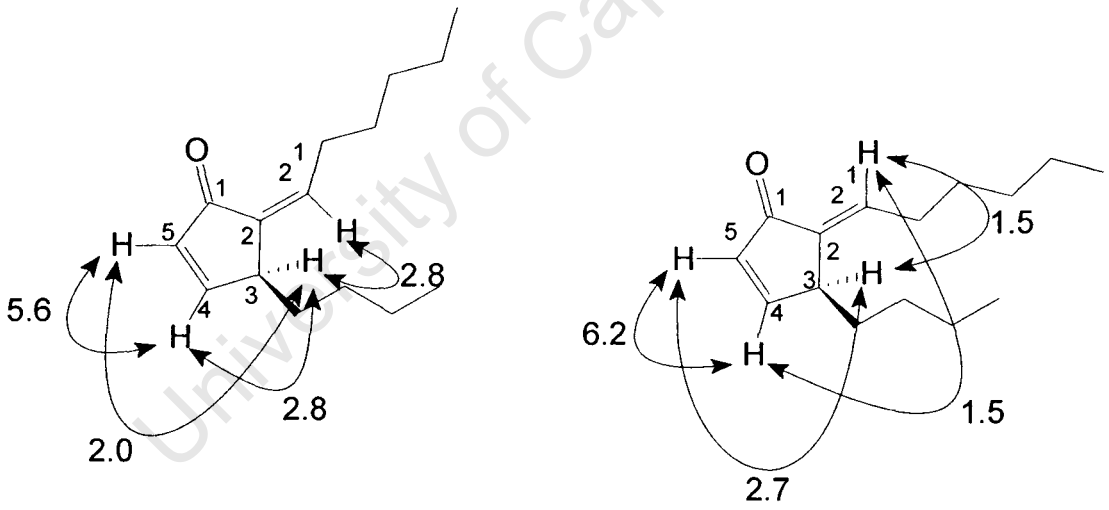
Figure 2.5 Selected coupling constants of **142**and **144** (*J* values in Hz).

Differentiation of the *E*- and *Z*-isomers of **145** and **144** was based on interpretation of the ^{1}H NMR in combination with structure modelling. A few key signals were used in this interpretation. The signal assigned to H-4 in **145** resonates as a ddd at δ 7.54 (*J* 6.2, 2.7 and 1.5 Hz). The same signal in **144** resonates as a dd at δ 7.63 (*J* 5.6 and 2.8 Hz). Structure modelling indicates that the extra coupling in **145** is due to H-4 interaction with H-2^1. This is only

possible in the *E*-isomer configuration. This small coupling does not occur in **144** as the *Z*-isomer is not structurally set up for such "W" coupling. This is confirmed by the signal H-2^1 which is shown to couple to H-2^2, H-3 and H-4. This coupling of H-2^1 to H-4 is not present in **144** as the protons are not optimally aligned for such a long-range coupling to occur. From the above data, it is clear that **145** is the *E* isomer while **144** is the *Z*-product.

Table 2.6 Selected chemical shifts and coupling constants for **144** and **145**

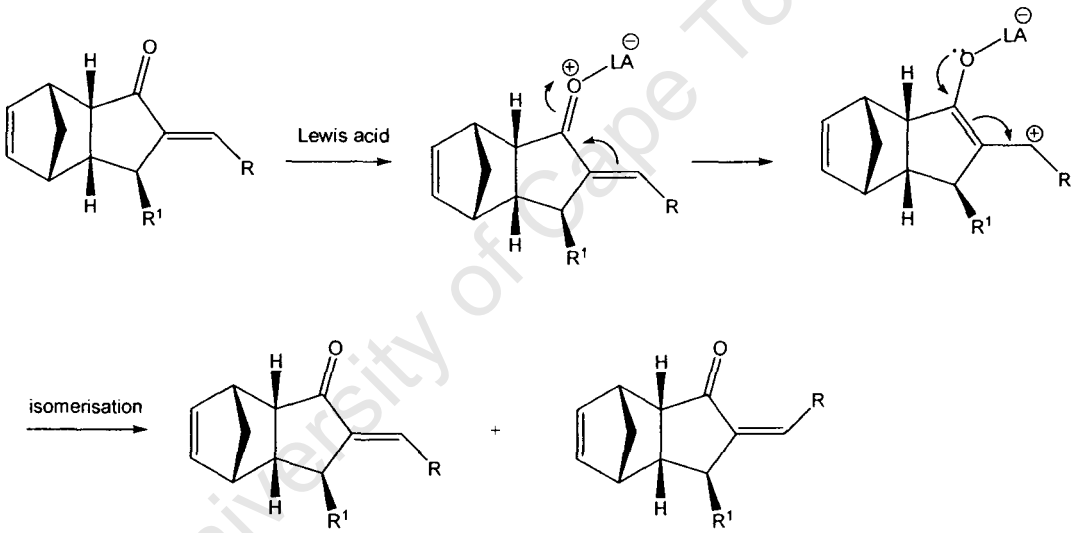
	H-2^1	H-4	H-5
145(*E*)	6.55 (tt, *J* 2 x 7.8 and 2 x1.5 Hz)	7.54 (ddd, *J* 6.2, 2.7 and 1.5 Hz)	6.32 (dd, *J* 6.2 and 1.7 Hz)
144(*Z*)	6.64 (td, *J* 7.8 and 2 x 2.8 Hz)	7.63 (dd, *J* 5.6 and 2.8 Hz)	6.14 (dd, *J* 5.6 and 2.0 Hz)



Z-isomer: **144** *E*-isomer: **145**

Figure 2.5 Selected coupling constants of **144** and **145** (*J* values in Hz).

Both starting materials for the rDA reaction **133** and **132** are diastereomerically pure *E*-isomers with no evidence indicating any *Z*-isomer present. The rDA reaction, however, is seen to yield a mixture of both *E*- and *Z*-products. This can only be rationalized by concluding that partial isomerisation occurs during the course of the rDA reaction resulting in the formation of both the *E*- and *Z*-isomers. Facile isomerisation of α, β-unsaturated ketones under both thermal[88] and photochemical conditions[89] has been reported in the literature. Lewis-acid complexation to the carbonyl oxygen is followed by electron migration to neutralise the positively charged oxygen. Regeneration of the α, β-unsaturated ketone could see neutralization of the positively charged CH_2 occurring from either face of the molecule (Scheme 2.26).

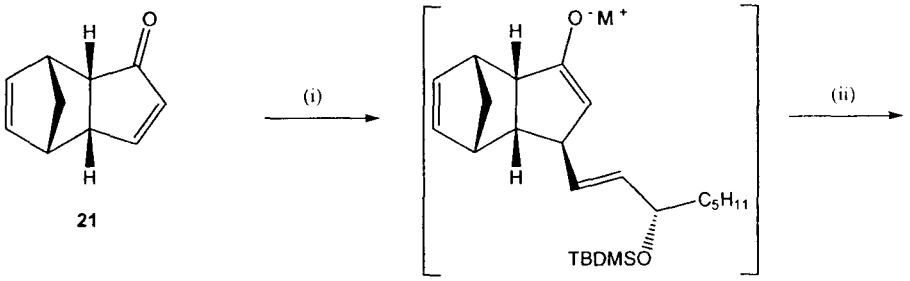


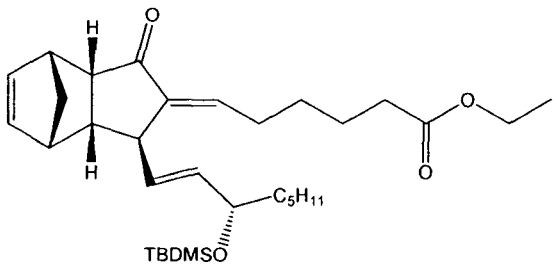
Scheme 2.26

Route C as described in Scheme 2.23 first involves an *exo* to *endo*cyclic double bond isomerisation. Attempts at the isomerisation of **134** with concentrated hydrochloric acid in the presence of *n*-BuOH[90] were unsuccessful, yielding only the starting three component addition product. A

second well known approach, which involves the use of zinc dust in the presence of acetic acid,[91] was attempted on **134** to effect this synthetic transformation. However, once again, stirring for 48 h only produced the starting material. Further efforts may involve the use of rhodium [92,93] or potassium fluoride in the presence of Al_2O_3[94] to render the *endo*cyclic isomerisation product **(137)**. It is then postulated that conjugate reduction of **20** will afford the *cis* vicinally disubstituted **138**. Lewis-acid mediated rDA conditions are expected to reveal the isoprostane moiety **139**.

This three component coupling approach was extended towards the use of **94** as the β chain, as is found in PG's A to J. Hydrozirconation of 1-alkynes using the Schwartz reagent provides a route towards stereochemical and regiochemical control of *E*-isomer formation.[95,96] The alkenylzirconate of the alkyne is transmetallated to give the cyanocuprate generated *in situ* as before (Scheme 2.8). Therefore conjugate addition of the cuprate to **21** inserts the β-chain and concomitantly generates the enolate species *in situ* which was then quenched with the aldehyde **95** to give **96** in low yield (Scheme 2.27). The ^{1}H NMR spectrum of the product has olefinic resonances at δ 6.01 (2H, m, H-8 and H-9), and δ 6.39 (1H, m) indicating that the postulated *exo*cyclic olefinic group had indeed been installed. The presence of signal at δ 6.39 ^{1}HNMR indicated the presence of a new olefinic signal which could only be ascribed to H-4^1. Attempts to generate this compound using base-mediated methodology have been indicated earlier (Scheme 2.8).





96

Scheme 2.27 *Reagents and conditions*: (i) $Cp_2Zr(H)Cl$ (ii) **93**, MeLi, CuCN, THF, -50 to 0°C, 4%.

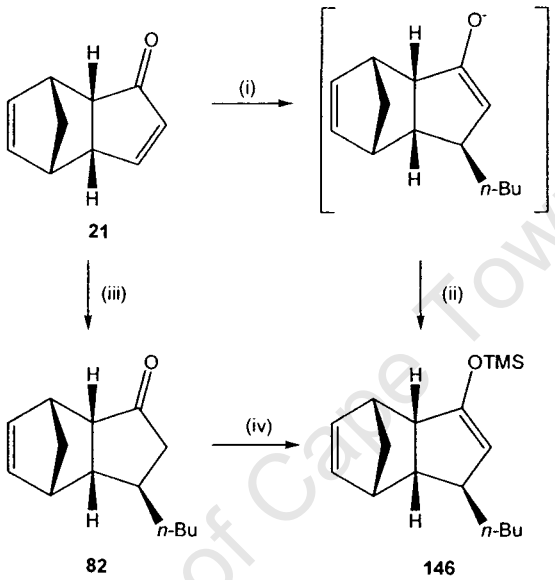
2.5 ENOL SILYL ETHER APPROACH

This indirect approach involving enol silyl ethers utilizes path C of Scheme 2.3. As previously describes this involves:

1) Formation of enol silyl ether *via* conjugate addition of R^1
2) Liberation of the enolate
3) Trapping of the enolate with the reactive α–sidechain

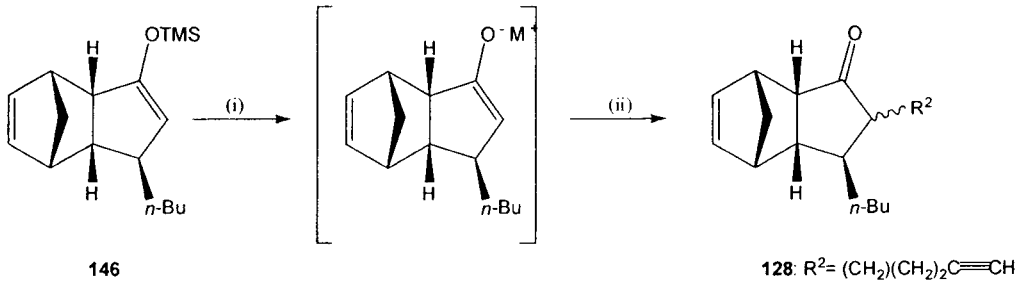
The enol silyl ether could be generated directly from **21** *via* cuprate mediated addition of the β-side chain and trapping of the resulting enolate as a TMS ether as in **146**. Alternatively, the butyl ketone **(82)**, upon treatment with a

base would give an enolate which could subsequently be trapped by TMSCl to give **146** (Scheme 2.28). Facile cleavage of the enol silyl ether on silica gel made purification and isolation difficult accounting for the use of crude enol silyl ether in many of these procedures. However, evaluation of the ^{1}H NMR of the crude material indicates the presence of the TMS ether group as well as the butyl chain. In order to overcome this difficulty, the enol silyl ether was prepared and used without further purification.



Scheme 2.28 *Reagents and conditions* : (i) *n*-BuLi, CuCN, THF, -78°C, (ii) TMSCl, THF, 0°C, 46%, (iii) : *n*-BuLi, CuI, Et_2O, 0°C to rt, 2 h, 62% (iv) LDA, THF, TMSCl, -78° to rt, 54%.

With the intermediate in hand, attempts were now made at α-sidechain insertion through liberating the enolate and quenching it with various R^2 groups. The first reactive group that was investigated was the triflate leaving group.



146

128: $R^2 = (CH_2)(CH_2)_2C{\equiv}CH$

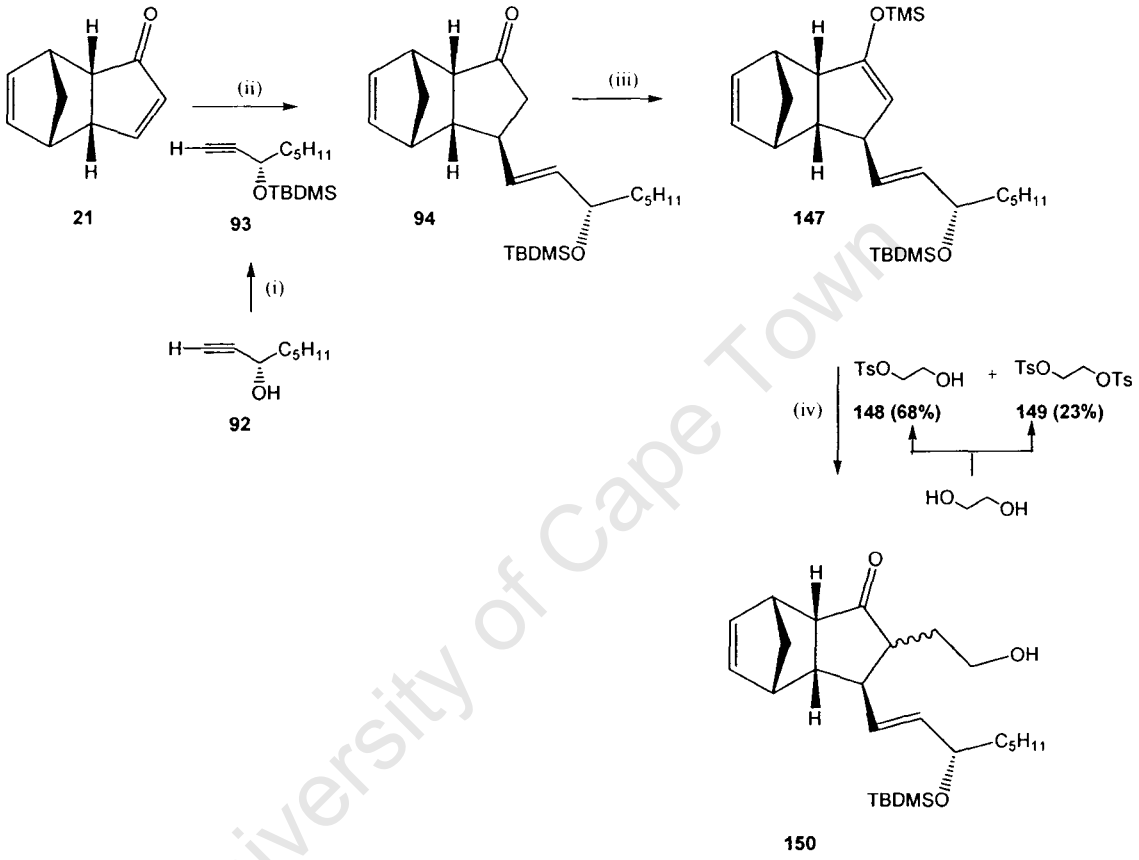
Scheme 2.29 *Reagents and conditions*: (i) MeLi, THF, -25°C, (ii) R^2-OTf, THF, -78 to -40°C, 13%.

Lithium enolate was regenerated from the enol silyl ether by treatment with MeLi in THF (Scheme 2.29). The triflate is simultaneously prepared by addition of Tf_2O to a mixture of the corresponding alcohol and 2, 6-ditert-butylpyridine. A volume of hexane equivalent to that of THF was added and the resulting solution stirred at -78°C which formed a suspension. This was then filtered to afford a clear solution of the triflate.

Several attempts were made to optimize the yields. The use of 2, 6-di-tert-butyl-4-methylpyridine as opposed to triethylamine as base in formation of the triflate, did not contribute to a greater conversion of the enolate to the product. These reactions were characterized by large amounts of decomposition and products appeared to be contaminated. While the reactions proceeded, the yields obtained were very low and over time the integrity of the triflate can become compromised which does not allow for extended reaction times.

In an attempt to generate the target PG analogues *via* this methodology, the lower PG sidechain was reacted with enone **21** to give **94**. In order to avoid the complications previously outlined associated with the use of vinyl stannane methodology, the Schwartz reagent is used to insert the β-chain and generate the required regiospecific enolate species as indicated above (page 34). Conjugate addition of the cuprate to **21** generates **94** (Scheme 2.30). LDA

treatment of **94** generates the required enolate which is then trapped by chlorotrimethylsilane to afford **147**. Crude **147** was treated with MeLi to generate the enolate which was quenched with the tosylate **148** to insert the α-chain.

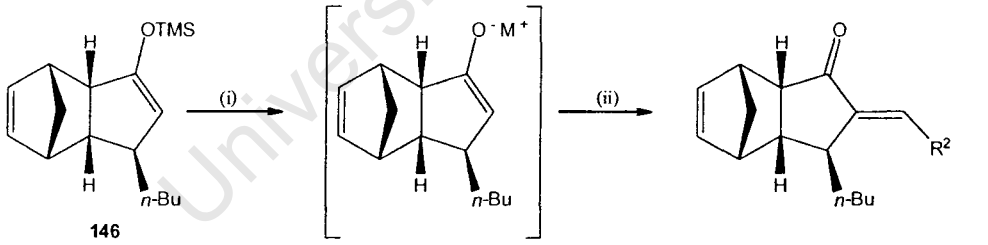


Scheme 2.30 *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, rt, 18 h, 78% (ii) $Cp_2Zr(H)Cl$, **93,** MeLi, CuCN, THF, -50 to 0°C,50% (iii) LDA, TMSCl, THF, -78 to rt (iv) MeLi, **148**, THF, -78 to-23°C, 5%.

While the resulting yield of the conversion of **147** to **150** is poor, NMR evidence indicates the presence of a hydroxyl group in the ^1H NMR which is further verified by the absorption band at 3673 cm^{-1} in the IR spectrum. The poor yield

can be explained by the fact that a large percentage of the enolate is being quenched by the alcohol. This can be attributed to the basic enolate being quenched by the hydroxyl group of **148**. Hence, a significant amount of **94** was isolated.

The following attempts involve the use of aldehydes to insert the α-sidechain. Generation of these adducts *via* a 3CC approach have been elucidated earlier (Schemes 2.14-2.27). Here we illustrate the success of installing the α-sidechain in a two step process as indicated in Scheme 2.28. The enolate generated from the corresponding enol silyl ether, is quenched with an aldehyde.[97,81] The enol silyl ether was treated with MeLi to release the enolate. This lithium enolate was transmetallated with zinc in the form of $ZnCl_2$.TMEDA. The enolate was then trapped with the aldehyde to insert the α-sidechain (Scheme 2.31). Highly regioselective alkylation of the enolate generated from the corresponding enol silyl ether only occurs when the enolate reacts with an alkylating agent prior to equilibration (Scheme 2.5)



146

151: R^2= $(CH_2)_4OTHP$ (28%)
133: R^2= $(CH_2)_4CO_2Et$ (65%)

Scheme 2.31 *Reagents and conditions*: (i) MeLi (for **151**) or BuLi (for **133**), $ZnCl_2$.TMEDA, THF, -25°C, (ii) R^2CHO, THF, -20°C to rt.

Table 2.7 Synthesis of *exo*cyclic enones *via* MeLi mediated enolate generation followed by aldehyde quench

Entry	Aldehyde	Product) Yield, %) (E/Z ratio)
1	$CHO(CH_2)_4OTHP$ **(152)**	**151** (28) (100:0)
2	$CO_2Et(CH_2)_4CHO$**(95)**	**133** (65)(100:0)

Entry 1 (Table 2.7) makes use of the aldehyde **(152)** which was synthesized in two steps from 1, 5-pentanediol. Formation of the mono-THP protected adduct as described previously (Scheme 2.10) was followed by Swern oxidation to give the aldehyde. Following the coupling reaction, the ^{1}H NMR spectrum of **151** revealed the presence of a signal at δ 6.30 (ddd, *J* 8.6, 6.8 and 2.0 Hz) in the ^{1}H NMR spectrum and at δ 143.8 in the ^{13}C spectrum indicates the presence of a newly installed olefinic moiety. Allylic coupling accounts for the coupling constant of 2.0 Hz for H-4[1]. The result is supported by verifying HRMS. Entry 2 uses **95** as the aldehyde for addition of the α-group. The aldehyde was synthesized from ethyl 6-hydroxy-hexanoate as described before (page 30-31). As opposed to the result obtained using the 3CC approach, using this approach the reaction does not exhibit a large number of by-products. The presumed intermediate β-hydroxy-ketone product is not identified and dehydration seems to take place almost instantaneously (**133**, Scheme 2.22). The structure of the product is identified and elucidated in the same manner as its 3CC counterpart (Scheme 2.22).

2.6 Conclusion

The three pronged approach outlined in this chapter serves to demonstrate that access to both cyclopentenone prostaglandins and their isoprostane analogues is possible employing the methodology we have developed. Furthermore, the synthesis of cross-conjugated dienones has been described. Further elaboration of this divergent strategy starting from common precursor **21** will yield an array of diverse molecules suitable for biological testing. The control of diversity is governed by the choice of sidechains employed.

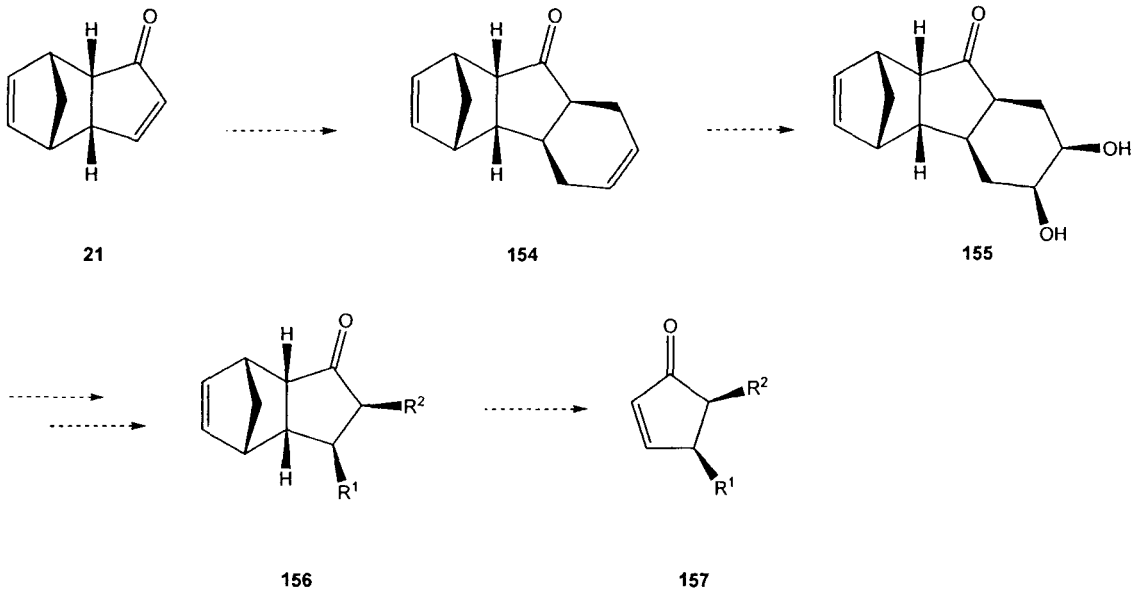
CHAPTER 3

CYCLADDITIONS WITH *OXODICYCLOPENTADIENE* AND *exo-3-HYDROXYDICLOPENTADIENE* AS DIENOPHILES

3.1 Introduction

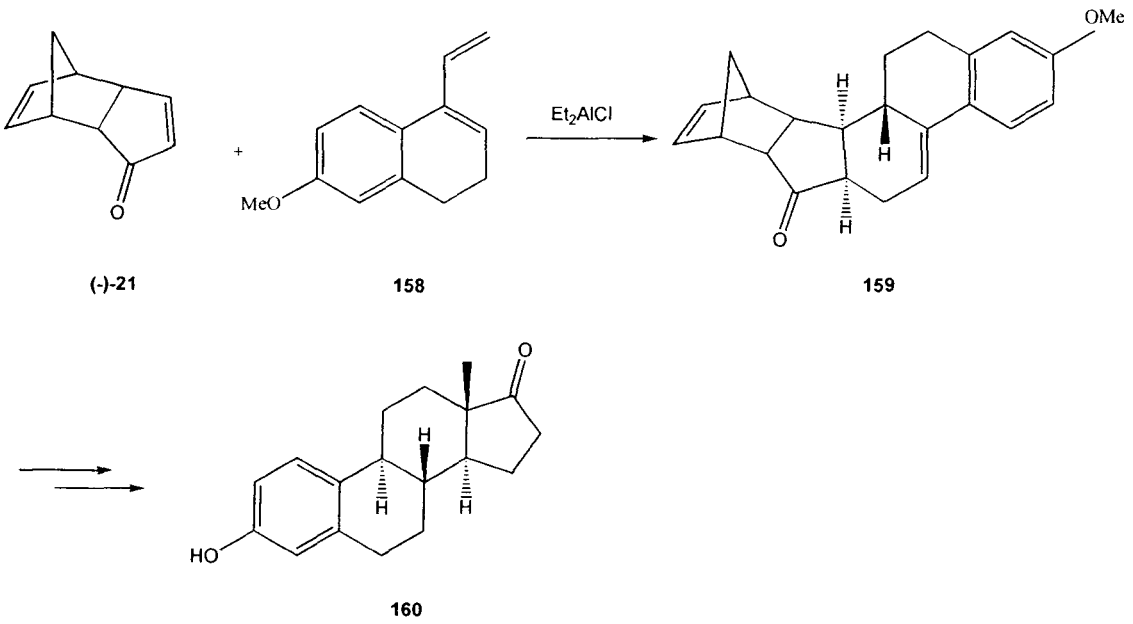
The Diels-Alder reaction is one of the most commonly encountered strategies for the formation of multiple carbon-carbon bonds in both a regio- and stereoselective manner. A survey of the literature revealed surprisingly few reports detailing the use of the tricyclic decadienone **21** as dienophile in the [4 + 2] Diels-Alder cycloaddition reaction. The paucity of examples may potentially indicate that **21** is in fact a poor dienophile. Nevertheless, these examples proved to be informative in directing our work in the area. Strategically, our aim was to generate iPG-type molecules (A) using a Diels-Alder reaction to install the requisite *cis*-orientated C4- and C5-sidechains.

The successful synthesis of the target compound **157** is dependant on the regio- and stereoselective cycloaddition of **21** with butadiene to produce **154** (Scheme 3.1). Regioselective *cis*-hydroxylation of **154** will afford **155** which will be transformed into **156** over a number of steps. A Lewis-acid catalysed rDA reaction performed on **156**, is envisaged to reveal the target compound **157**.



Scheme 3.1 Proposed synthetic plan for the synthesis of **157** from **21**.

The utility of **21** as a dienophile has been demonstrated as a key first step in the diastereoselective synthesis of (+)-estrone **(160)** (Scheme 3.2).[98] This elegant synthesis makes use of chiral **21**, which is accessible from racemic cyclopentadiene *via* lipase mediated asymmetric resolution [99,100] [101], and 6-methoxy-1-vinyl-3,4-dihydronaphthalene **(158)**. These are reacted under Lewis-acid conditions to give the cycloadduct **(159)**. A four step sequence which included thermolysis as a key step revealed estrone **(160)**.

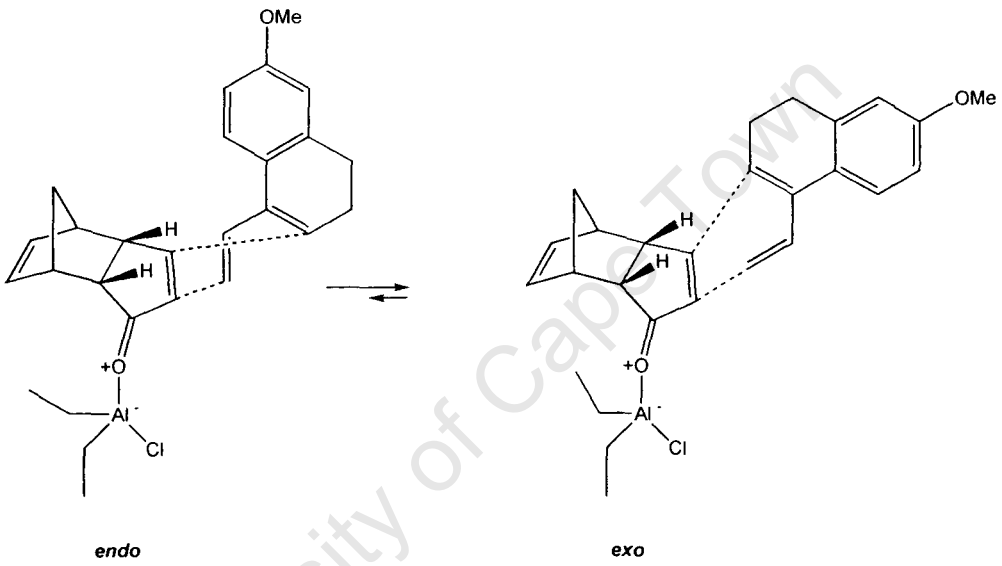


Scheme 3.2 Diels Alder cycloaddition mediated synthesis of (+)-estrone **160**.

It is recognized that the Alder *endo*-rule governs the stereochemical outcome of a Diels-Alder reaction. Lewis-acid catalysts are known to enhance regioselectivity in these cycloaddition reactions *via* complexation to the dienophile. This interaction is said to reduce the energy gap between the lowest unoccupied molecular orbital (LUMO) of the dienophile and the highest occupied molecular orbital (HOMO) of the diene. This decreases the activation energy required for the cycloaddition. This stabilization is greater in the *endo*-transition state than the *exo* transition state thus the use of Lewis-acids has been shown to favour *endo*-mode of addition over the *exo*-mode. Quinkert noted that the Lewis-acid may not only influences the reaction rate but also the topology of the transition state structure[102] while, in a comprehensive review, Nicolaou and co-workers commented on the ability of a Lewis-acid to reverse the regiochemical outcome of a Diels-Alder addition reaction and generate products that would not have been observed in simple, thermally induced

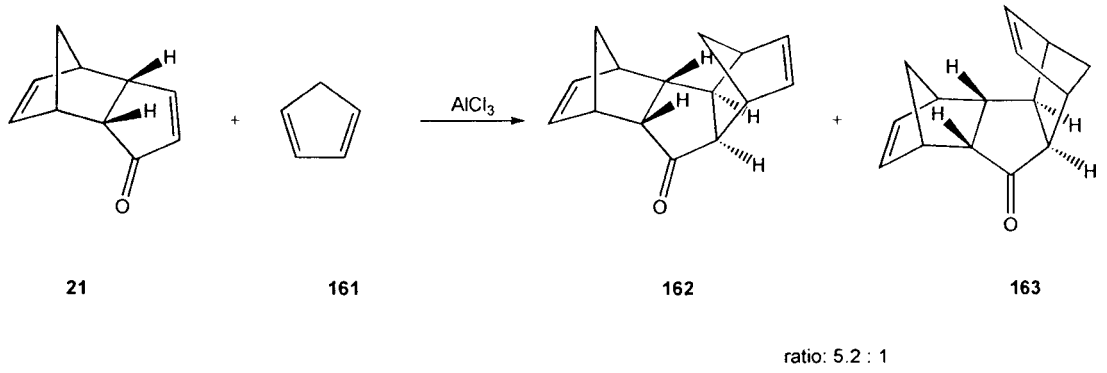
reactions. The expectation is thus that the *endo*-addition of a dienophile to a diene is favoured.[103]

In the reaction detailing the formation of estrone, however, complete and yet opposite stereoselectivity was observed. This has been attributed to the 'preferential intervention' of the *exo* mode of addition as opposed to the electronically favoured *endo* mode to alleviate steric strain which accompanies the *endo*-addition (Scheme 3.3). [104]



Scheme 3.3 Lewis-acid interaction with dienophile.

Following work by Cookson and co-workers,[105]Zwannenberg *et al*[106]have observed the stereoselective *exo*-addition of **21** with cyclopentadiene. The reaction, carried out in the presence of $AlCl_3$, afforded both the *endo*-and *exo*-cycloadducts with a strong preference for formation of the *exo* cycloadduct being exhibited (Scheme 3.4).

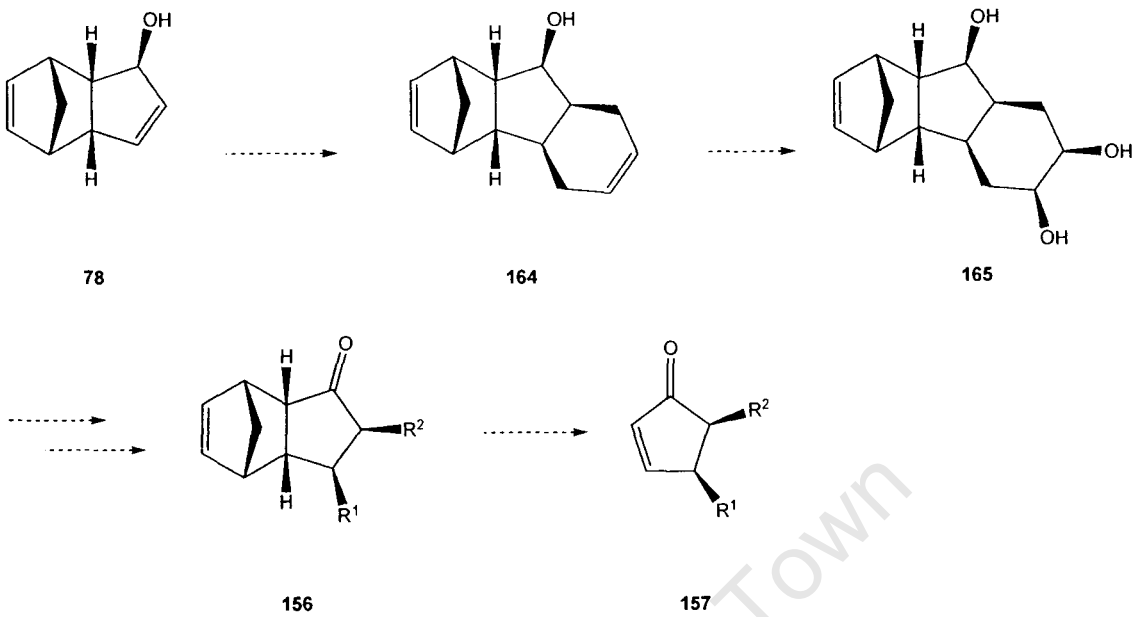


Scheme 3.4 Diels Alder cycloaddition of **21** and cyclopentadiene.

Their attempts at a thermal Diels-Alder cycloaddition *i.e.* without the use of a Lewis-acid catalyst proved unsuccessful.

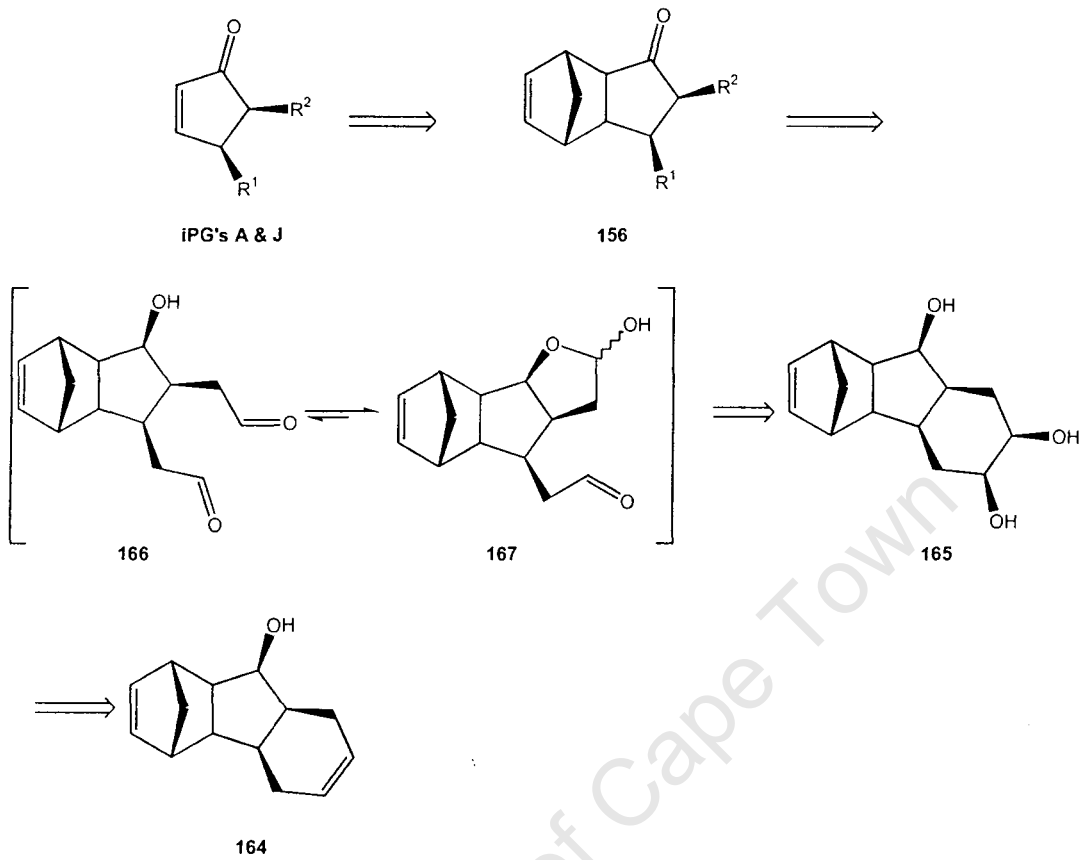
In light of the aforementioned literature precedence and the previously proposed hypothesis, which invokes the architecture of **21** as the dominant feature controlling the stereochemical outcome of additions (Scheme 2.2), the concept of utilizing the Diels-Alder cycloadduct as a key intermediate in the synthesis of the targeted prostaglandin analogues was considered worthy of investigation.

Our investigation into the thermal and Lewis-acid catalysed cycloadditions of **21** with butadiene and Danishefsky's diene was characterized by low yields and large decomposition. In light of the inability to produce the cycloadduct in sufficient quantities for the development of this synthetic route, our focus was redirected towards employing the alcohol **78** as dienophile. While in theory this is electronically considered to be a less likely dienophile than **21**, the Diels-Alder addition afforded a clean, stereoselectively privileged cycloadduct **(164)** (Scheme 3.5). The cycloadduct **(164)** contains an array of functional groups ideally positioned for conversion to the prostaglandin analogues. The proposed synthetic plan follows precisely as described earlier with the exception of including an oxidation of the alcohol to the enone in the conversion of **165** to **158**.



Scheme 3.5 Proposed synthetic plan for the synthesis of **157** from **78**.

The key transformations are outlined in the retrosynthetic analysis of iPG's A and J (Scheme 3.6).



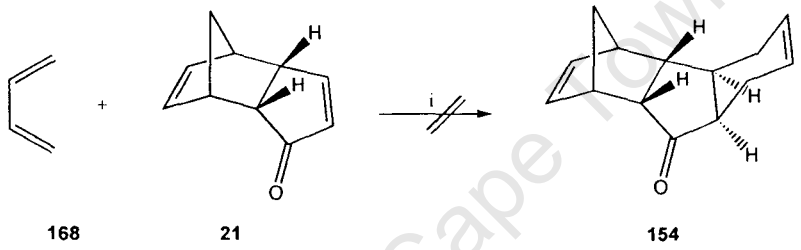
Scheme 3.6 Retrosynthetic analysis for the conversion of **164** to PGA-J.

In examining the retrosynthetic analysis, it was envisaged that a Lewis-acid catalysed retro Diels-Alder reaction of **157** would reveal the α, β-unsaturated cyclopentenone of PG's A and J. The following key step that was identified, involves homologation of **167** using Wittig methodology to give R^1 and R^2 as illustrated in **157**. Ready lactolisation of the α-sidechain carbonyl moiety of **166** to **167** would allow chemodifferentiation of the carbonyl functionalities. This would be exploited to extend both chains differentially. It was thought that oxidative cleavage the triol **(165)** would afford **166**. Initial *cis*-hydroxylation of the cycloadduct would reveal the triol that was required.

3.2 RESULTS AND DISCUSSION

3.2.1 Cycloadditions of *oxodicyclopentadiene* (21) with butadiene

Various methods for the generation of this cycloadduct were attempted. Initial attempts focused on the use of the thermally induced Diels-Alder cycloaddition between the enone **(21)** and butadiene **168**. These compounds were heated in a sealed pressure tube in toluene at 160°C for 24 hours. This demonstrated that under these conditions, the attempted transformation to the cycloadduct yielded only starting material (Scheme 3.7).

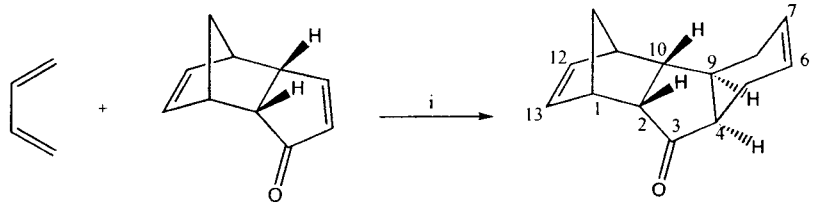


168 21 154

Scheme 3.7 *Reagents and conditions:* (i) toluene, 160°C, 24 h.

The Diels-Alder adduct reaction between **21** and butadiene **168** under Lewis-acid catalysed conditions provided erratic results. An excess of butadiene was condensed into toluene. The enone **(21)** and Lewis-acid were added and the mixture stirred for 21 h in a sealed pressure tube. These reactions were performed using a number of different Lewis-acids in varying molar equivalents. The yields of the cyclization products were dependant on the choice of Lewis-acid used. Some of these results have been tabulated below (Scheme 3.8). The reactions were characterized by the production of complex mixtures which were often difficult to separate as well as an inability to drive the reaction to completion. As noted by Roush *et al*, that while the best product ratios are generally obtained with use of Lewis-acids, there are a number of

substrates which decompose and fail to undergo cycloaddition reactions upon exposure to Lewis-acid reagents.[107]



168 21 154

Compound	Lewis-acid	No. of Equiv.	% yield
154	BF_3OEt_2	1.0	18 %
154	$TiCl_4$	0.2	33 %
154	$SnCl_4$	0.2	18 %

Scheme 3.8 *Reagents and conditions:* (i) toluene, -78°C to 25°C, 21 h.

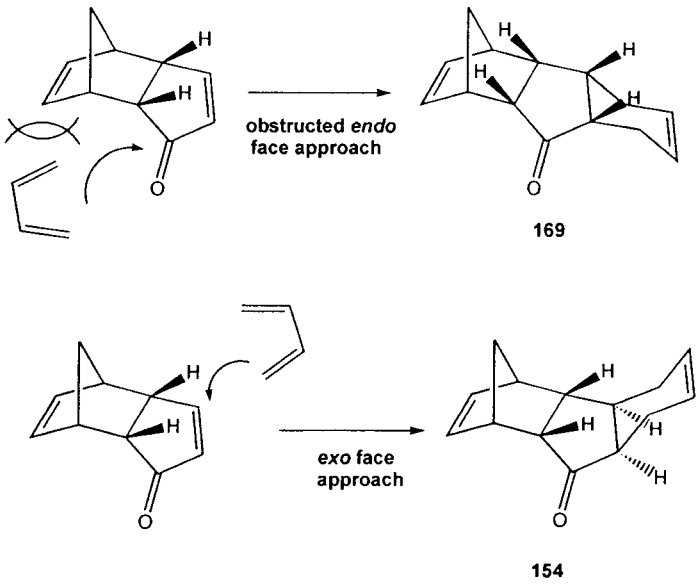
Mass spectral, and NMR spectral data were consistent with the assigned structure of the cycloadduct. Although yields of the cyclodducts obtained were poor, only one stereoisomer was detected. The signal for H-6 and H-7 resonated at δ 5.68 (2H, m) while those for H-12 and H-13 appeared at δ 6.10 and δ 6.24. Here, H-12 and H-13 are shifted downfield relative to their positions in the starting enone **21**. Zwannenburg *et al* in their synthesis of **162**, report similar chemical shifts for these olefinic protons (δ 6.14 and 6.17).[106]

Rationalization of the chemoselectivity could be inferred from the available spectral data. H-4 has been identified to be the most deshielded proton in the starting enone and resonates at δ 7.36. The disappearance of this signal in **154** is evidence that addition has taken place at the H-4/H-5 position of the enone. This result is to be expected. The proximity of the C-10 bridge has a subtle

influence on the chemoselective outcome of the Diels-Alder reaction. Furthermore, this is the more likely dienophilic position. Due to conjugation with the carbonyl group, it is less electron rich than its non-conjugated counterpart. For all these reasons, it was assumed, and shown, that addition would occur to give the assigned product.

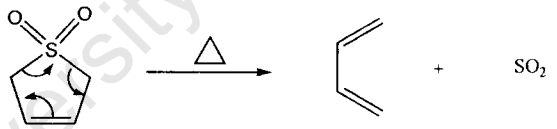
The proposed stereoselectivity can be explained in terms of the concave structure of **21** which leads to the formation of the sterically favoured *exo*-isomer over that of the electronically favoured *endo*-isomer (Scheme 3.9). For the electronically favoured *endo*-addition to occur, the diene would have to add at the sterically congested or hindered concave face of **21**. This steric interference directs the diene towards the more accessible *exo*-face of the molecule promoting the formation of the electronically less favoured but sterically more favoured *exo* product. Our architectural hypothesis combined with the spectroscopic findings provides convincing proof that this is indeed the case.

Literature precedent for these kinds of reactions points towards the use of Lewis-acids in the Diels-Alder cycloaddition with the tricyclic dienone **(21)** as dienophile. There are however few examples of this nature available for study which may indicate a level of difficulty involved in successfully implementing this chemical transformation.



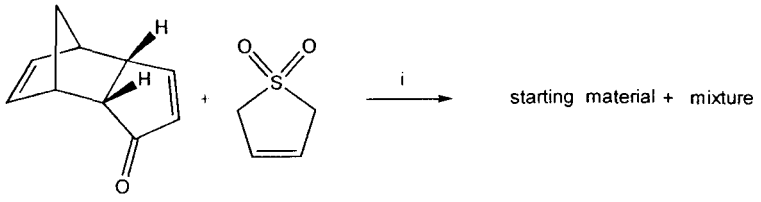
Scheme 3.9 Steric effects exerted by the architecture of **21** on the stereochemical outcome of the Diels-Alder cycloaddition.

Our investigations led to the use of butadiene sulfone as diene, which provides butadiene *in situ* which is released by extrusion of SO_2 under high temperature conditions (Scheme 3.10).



Scheme 3.10 Generation of butadiene from butadiene sulfone.

The thermal cycloaddition of the dienone **(21)** with butadiene sulfone **(170)** was investigated (Scheme 3.11). The most successful result afforded a mixture of inseparable products with less than 50 % conversion of the starting material occurring after 6 days. The complexity of the product mixtures obtained using this strategy render it unsuitable for the preparation of these cycloadducts as a key intermediate in this synthesis.



21 170

Scheme 3.11 *Reagents and conditions:* (i) heat, toluene, 18 h to 6 days

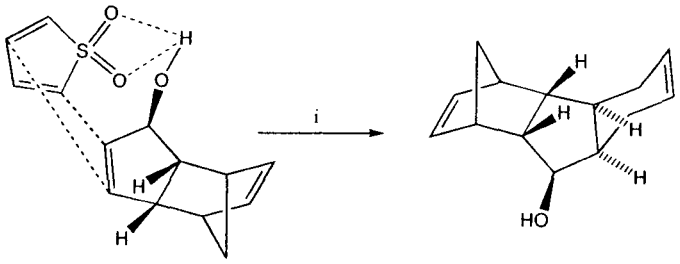
Employing similar methodology with the addition of a Lewis-acid also proved unsuccessful. $ZnCl_2$.TMEDA provides a source of deliverable $ZnCl_2$ and ensures the integrity of the Lewis-acid delivered to the dienophile during the reaction. This procedure, however, was not encouraging as it resulted in no conversion to the cycloadduct after 24 hours.

3.2.2 Cycloadditions with 3-*exo-hydroxydicyclopentadiene* (78) as dienophile

We turned our attention to the use of the alcohol **(78)** as the dienophile. While allylic alcohols are considered to be unactivated dienophiles, there are examples in the literature where it has been successfully engaged as a dienophile. In a publication by Batey *et al*, they demonstrate the successful utilization of allylic and homoallylic alcohols as dienes in an intramolecular Diels-Alder reaction of 1, 3-dienylboronates under thermal conditions.[108] In ionic Diels-Alder reactions, allylic alcohols and ethers have been shown to be useful precursors as dienophilic allyl cations.[109]

While this is electronically a less likely dienophile than **21**, it was envisaged that, with the use of butadiene sulfone as diene, a hydrogen bonding

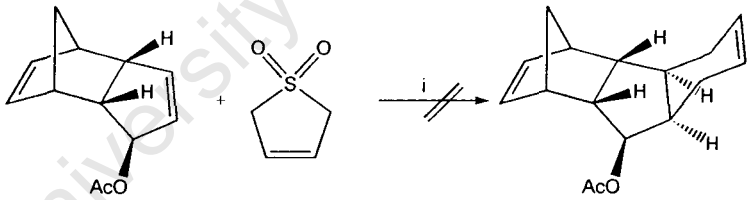
interaction between the hydroxyl proton and the oxygen of the sulfone would assist preorganising the reagents thus facilitating this reaction (Scheme 3.12). To this end, **78** was heated in toluene at 160°C for 2 hours which delivered **170** in 72 % yield. The successful outcome of this reaction was reproducible.



21 164

Scheme 3.12 *Reagents and conditions:* (i) heat, toluene, 160°C, 2 h, 72%.

This proposed theory was further substantiated by the fact that the acetate **77** when reacted with butadiene sulfone **(170)** in the same manner, showed no conversion to the product (Scheme 3.13).

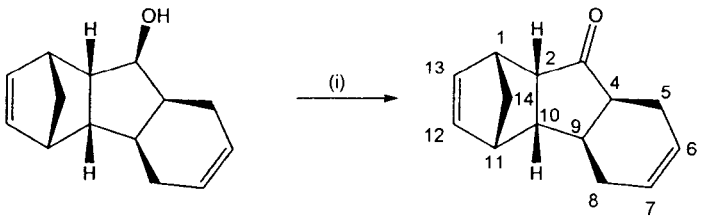


77 170

Scheme 3.13 *Reagents and conditions:* (i) heat, toluene, 160°C, 21 h.

Spectroscopic and analytical evidence confirmed the structure of **164** but absolute chemo- and stereochemistry was difficult to definitively assign due to the complex nature of the NMR spectrum. Hence, **164** was oxidized to the corresponding ketone **(154)** (Scheme 3.14). The ^{1}H NMR was used to

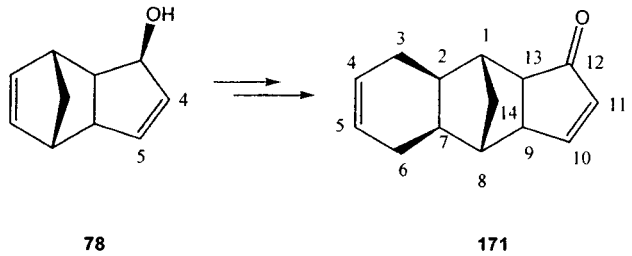
unequivocally confirm the chemoselectivity indicating that the cycloaddition reaction had indeed taken place at C-4 -C-5 double bond of the alcohol **78**. H-6 and H-7 are seen to resonate at δ 5.78 (ddd *J* 9.5, 4.7 and 1.3 Hz) and δ 5.84 (ddd, *J* 9.5, 5.2 and 0.9 Hz) while H-12 and H-13 resonate as a multiplet at δ 5.94 Hz.



164 **154**

Scheme 3.14 *Reagents and conditions*: (i) Dess Martin periodinane, CH_2Cl_2, 25°C, 56%.

The presence of H-6 and H-7 is diagnostic as had cycloaddition occurred at the alternative olefinic bond to give **171** (Scheme 3.15), the presence of protons relating to the α, β-unsaturated moiety of the cyclopentane would clearly be evident with the much deshielded resonance of H-10 occurring in the region δ 7.2-7.4 ppm. H-5 of **21** resonates at δ 7.36. Comparison to the ^{1}H NMR spectrum of **154** reveals that the two compounds are identical serving as further confirmation.



78 **171**

Scheme 3.15 Alternative chemoselective product.

3.3 Further Transformations on 164

Further chemistry focused on the identifying protocols for the transformation of **164** to the isoprostanes of PG's A and J as indicated in Figure 3.1.

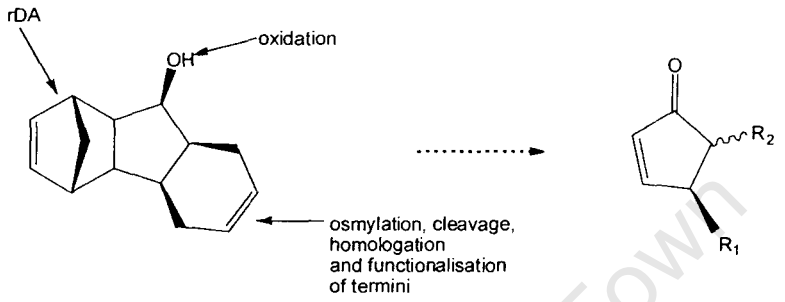
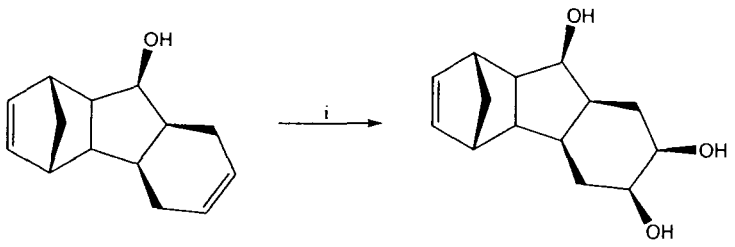


Figure 3.1 Transformations required in converting **21** to into PG's A and J.

The retrosynthetic analysis (Scheme 3.5) highlighted the proposed intermediates in the synthesis plan. A description of the progress made towards this end is described below.

Cis-hydroxylation

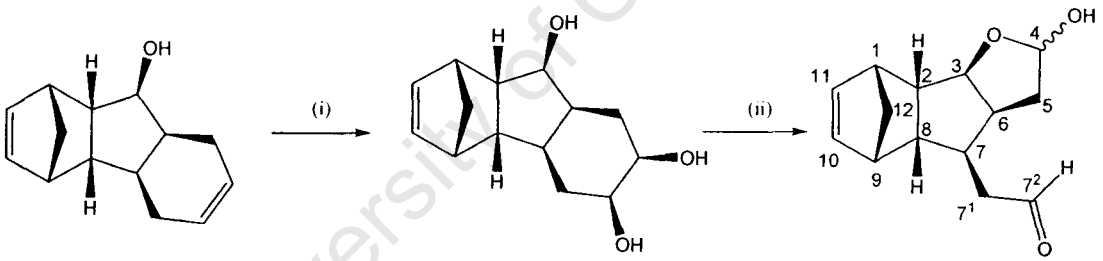
Cis-hydroxylation of the cycloadduct **164** utilized catalytic osmium tetroxide with *N*-morpholine-*N*-oxide as co-oxidant in acetone-water to give the triol **165** (Scheme 3.16).



164 165

Scheme 3.16 *Reagents and conditions:* (i) OsO_4, NMO, $(CH_3)_2CO$-H_2O, 25°C.

Having proven that the *cis*-hydroxylation could be successfully affected and noting that the triol was difficult to handle given its polarity, an approach in which *cis*-hydroxylation is directly followed by oxidative cleavage without isolation was of the cyclohexanetriol **(165)** was adopted. Thus Ogasawara *et al*[110] have documented a procedure which reported very acceptable yields utilizing this methodology. As such the crude cyclohexanetriol was successfully cleaved with lead tetraacetate in dichloromethane to yield the lactol **(167)** (Scheme 3.17).



164 165 167

Scheme 3.17 Tandem osmylation of **164** followed by oxidative cleavage to give **167**

The ^{1}H NMR of **167** provides diagnostic signals for confirmation of the proposed structure. Firstly, the presence of H-10 and H-11 has been confirmed by the presence of a multiplet, integrating for two protons, resonating at δ 5.73 and δ 5.74. The signal for H-4 resonates at δ 5.35 (dd, *J* 3.9 and 3.2 Hz) and has couplings to the two protons at the 5-position. This downfield shift is

expected for a proton adjacent to a hydroxyl group. The signal assigned to H-3 resonates as a doublet of doublets at δ 5.14 with couplings to H-2 and H-6. The presence of the aldehyde is confirmed by the signal resonating at δ 9.94, an expected chemical shift for an aldehyde proton as well as the resonance at δ 202.8 in the ^{13}C NMR spectrum.

3.4 Conclusion:

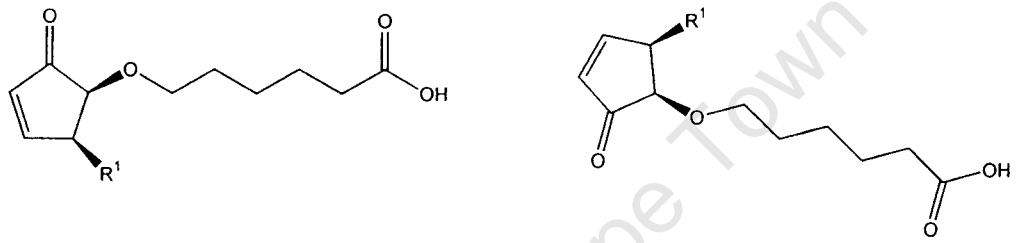
As indicated earlier (Schemes 3.5 and 3.6), the isolation of **167** provides the requisite *cis*-dialkyl stereochemistry of the two sidechains of the proposed PG targets. Simultaneously, it allows for chemoselective differentiation of these two sidechains for their extension. Installation of the α–sidechain (as seen in Chapter 2) is no longer necessary as it is built into the molecule. This also assists in circumventing the problem of epimerisation associated with moieties α to a carbonyl group. Elaboration of the sidechains using chemistry outlined by Larock *et al*[111] and Corey is envisaged to render the target prostaglandin analogues.

CHAPTER 4

SYNTHESIS OF OXYGEN ANALOGUES

4.1 Oxygen Analogues of cyclopentenone prostaglandins:

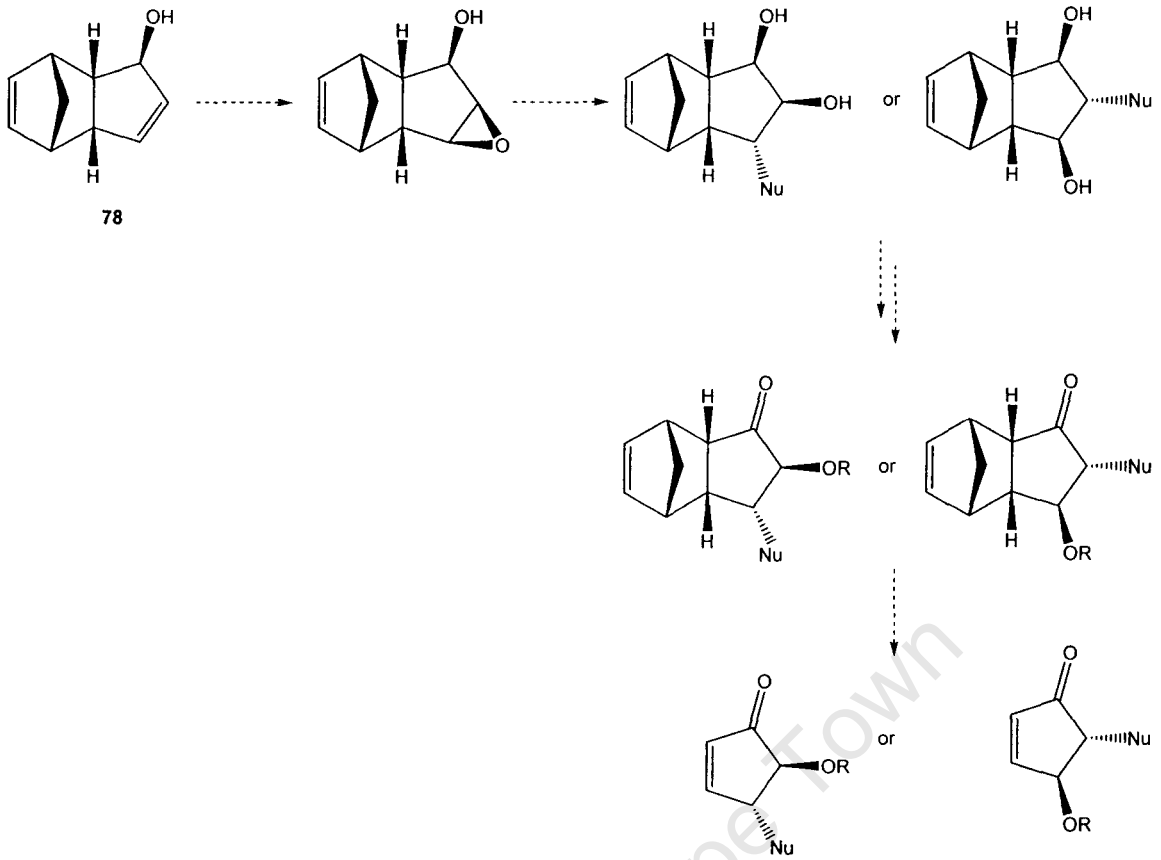
Within the scope of this project we sought to explore routes to oxygen analogues of the proposed targets of the cyclopentenone prostaglandins of the A- and J-series (Figure 4.1).



Oxo-PG-A Oxo-PG-J

Figure 4.1 Proposed Oxygen Analogues of the A and J series.

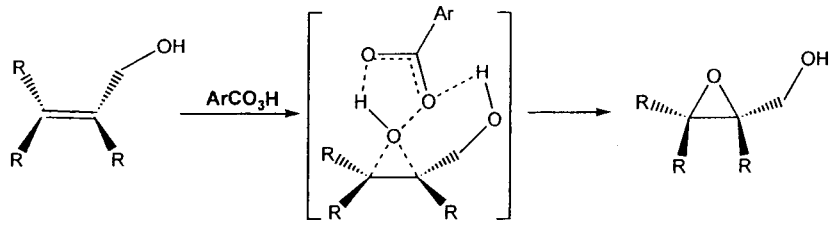
It was envisaged that epoxidation of **78** would yield the *cis*-epoxide utilizing the well known *cis*-directing effects of allylic alcohols. The regioselective opening of the epoxide was investigated as a means of installing one of the sidechains. This would render a free hydroxyl group for manipulation to introduce the second sidechain to reveal analogues of the type we are interested in.



Scheme 4.1 Proposed synthetic strategy.

The *cis*-directing effects of allylic and homoallylic alcohols are well documented in the literature.[112-114] Henbest and Wilson first observed that treatment of cyclic allylic alcohols with peracids resulted in epoxide formation *cis* to the hydroxyl group.[115] It has been postulated that the participation of the hydroxyl group results in delivery of the electrophilic oxygen to the nucleophilic alkene face *cis* to the hydroxyl group. This face selectivity with allyl alcohols has been attributed to hydrogen bond formation between the allyl hydroxyl group and the most basic carbonyl oxygen of the peroxy acid resulting in a transition state resembling the Bartlett "butterfly " mechanism[116] (Scheme 4.1). Henbest *et al* did however note that this directing effect is weak and thereby subject to steric interference for several allylic alcohols.[115]

The use of transition metals as catalysts for epoxidation has been documented.[117] Sharpless and Michaelson[118] have demonstrated the synthetic utility of vanadium and molybdenum as catalysts for this reaction. They have further shown that vanadium and molybdenum catalysed epoxidations of allylic and homoallylic alcohols are stereospecific, at times in contrast with the results obtained using peracids for the same transformation.

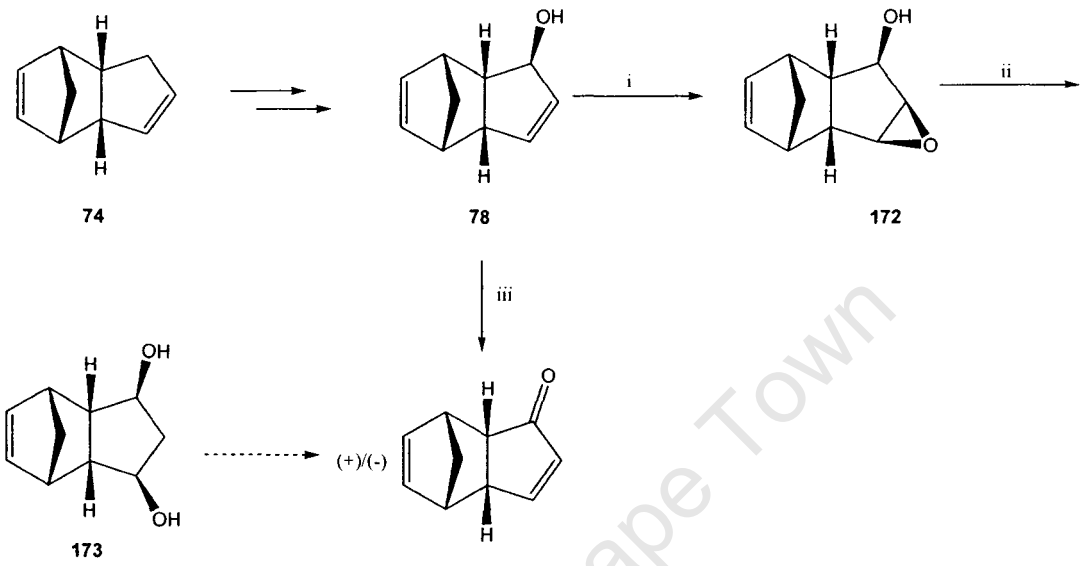


Scheme 4.1 Transition state resulting in delivery of peracid.

The alcohol **(78)**, generated from dicyclopentadiene **(74)**, (Scheme 2.3), was chemoselectively epoxidised with $VO(acac)_2$ in toluene to yield **172** (Scheme 4.2). The epoxidation results in the formation of the *exo*-epoxide. This can be attributed to the steric directing effects of the architecture of the molecule and the accessibility of the *exo*-face. This works in concert with the *cis*-directing effects of the allylic alcohol to produce the *exo*-epoxide.

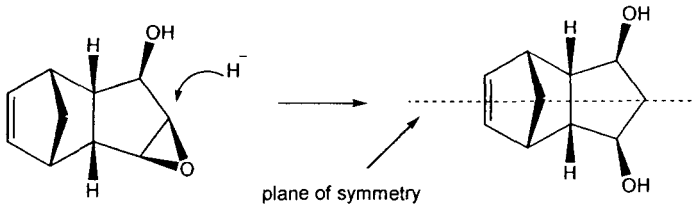
Spectroscopic data were consistent with the assigned structure of **172**. It's ^1H NMR spectrum showed the disappearance of two olefinic signals whilst the signals at δ 3.28 and δ 3.43, each integrating for one proton, indicated the presence of two new protons attached to the hydroxyl bearing carbons. The proton signal at δ 3.28 has been assigned to H-5 and resonates as a doublet. This is a result of a dihedral angle of nearly 90° between H-5 and H-6 resulting in J=0 for that interaction. The ^{13}C spectrum similarly showed the disappearance of the two olefinic signals relative to the starting alcohol. New

resonances at δ 63.4 and 62.8 concurred with the findings from the proton spectrum. The IR absorption band at 1221.7 supported the C-O stretch while an absorption band at 3019.0 indicated the presence of hydroxyl functionality. Attempts to affect the epoxidation using *m*-cpba rendered only **21**, presumably *via* oxidation of the hydroxyl group to the ketone.



Scheme 4.2 *Reagents and conditions:* (a) $VO(acac)_2$, *t*-BuOOH, toluene, rt to reflux, 40 min, 70 % (ii) LAH, THF, rt to reflux, 2 h, 76 % (ii). *m*-cpba, $CHCl_3$, reflux, 3h.

The epoxide **(172)** was opened *via* hydride attack at position 4 to give the *meso*-diol **(173)** (Scheme 4.3). Evidence in support of the proposed structure was derived from the ^1H NMR spectrum of **(173)**. Given that the *meso*-diol is C_2 symmetric, the spectrum revealed a simplification of the signals consistent with the formation of a *meso*-diol.

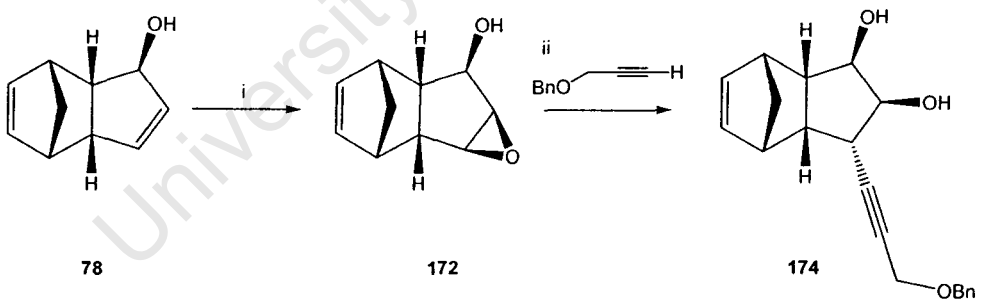


22 173

Scheme 4.3

Having demonstrated that opening of the *exo*-epoxy alcohol was feasible we sought to investigate this opening using other nucleophiles. The literature has numerous examples of $BF_3.Et_2O$ promoted reactions of organolithiates with epoxides.[119-121] Yamaguchi et *al* have shown that the combination of organolithium with BF_3Et_2O is well set up for the ring opening reaction of oxiranes and oxetanes.[122]

Following literature procedures, treatment of the epoxide **172** with the anion derived from the reaction with alkyne with *n*-BuLi and $BF_3.Et_2O$ in THF resulted in successful opening of the epoxide at C-5. This however only yielded the diol **(174)** in 9.5 % (Scheme 4.4) with recovery of the starting epoxide.



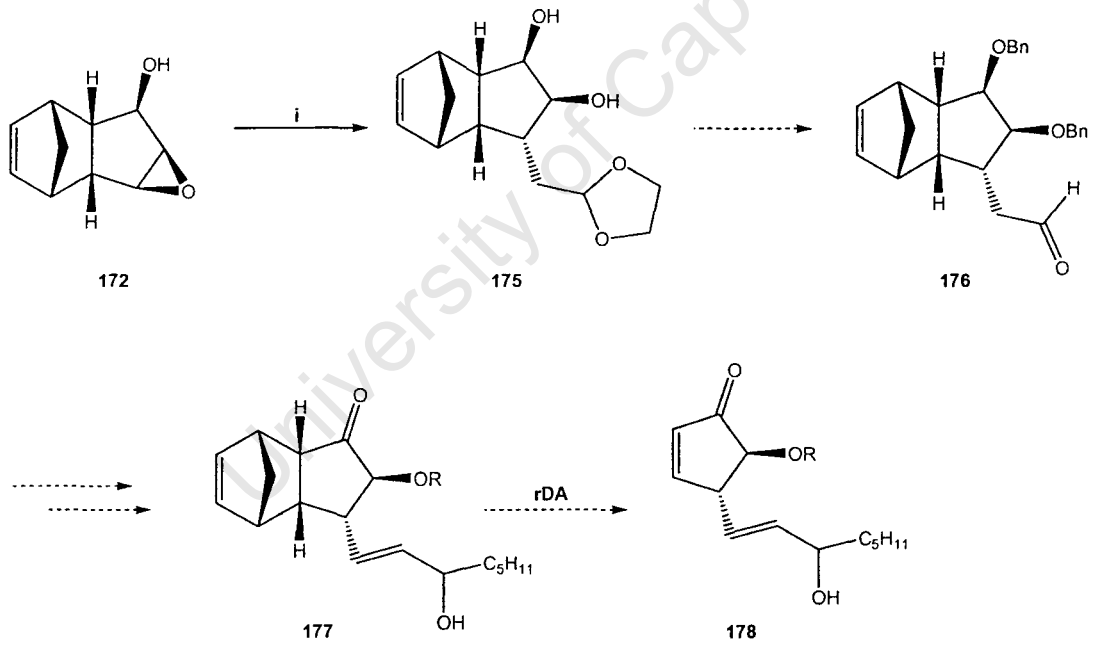
78 172 174

Scheme 4.4 *Reagents and conditions:* (a) $VO(acac)_2$ *t*-BuOOH, toluene, rt to reflux, 40 min, 70 % (b) *n*-BuLi, $BF_3.Et_2O$, THF, 78 to 0°C, 24 h, 9.5 %.

The regioselectivity is different to the opening by the hydride anion and can be attributed to the size of the incoming nucleophile. Fang *et al* indicate that, in the

case of a 2-substituted oxirane, ring opening usually occurs at the less hindered site.[123] The regioselectivity of the opening was confirmed by spectroscopic data. The ^{1}H NMR spectrum reveals the absence of a *meso*-diol confirming that ring-opening occurs *via* attack of the nucleophile at C5.

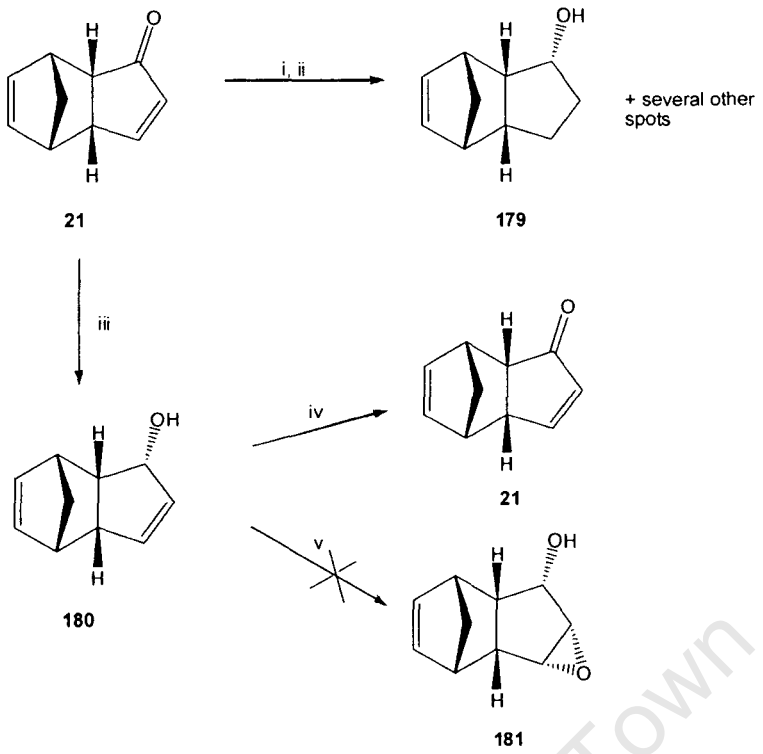
Further attempts at the regioselective opening of the *exo*-epoxide focused on the use of the Grignard reagent generated from 2-bromomethyl-1,3-dioxolane. Once installed, the dioxolane would then serve as a substrate for extension to the relevant sidechain (Scheme 4.5). Grignard addition of 2-bromometylmagnesium 1, 3-dioxolane successfully opened the epoxide **(172)** at C5 rendering the diol **(175)** in 10% yield (Scheme 4.5). Once again, this is confirmed by spectroscopic data revealing the absence of a *meso*-diol as well as the characteristic signal for the proton attached to C5.



Scheme 4.5 *Reagents and conditions* (i) 2-bromomethyl 1,3-dioxolane, Mg turnings, THF, rt-50°C, 8h.

Benzyl protection of the free hydroxyl groups and deprotection of the aldehyde was thought to be the first step in pursuing the synthesis. It was envisaged that deprotection of this suitably protected dioxalane will yield the aldehyde which can be extended using Wittig methodology to yield the β-sidechain. Chemoselective debenzylation and extension will afford the α-sidechain. Oxidation of the deprotected 3-hydroxy group at position 3 followed by a rDA will yield the proposed target.

While having demonstrated that the opening of the *exo*-epoxide could be achieved for installation of the required sidechains, in light of the difficulty in achieving complete conversion and hence acceptable synthetic yields, we turned our attention to the synthesis of the *endo*-epoxide to be obtained from epoxidation of the corresponding *endo*-alcohol. In this case, the architecture of the starting alcohol and the *cis*-directing effects the allylic alcohols no longer work in concert. It was predicted that regioselective opening of the *endo*-epoxide would prove to be more facile as nucleophilic attack would be favoured with the incoming nucleophile experiencing unhindered approach from the sterically less congested *exo*-face. Envisaged chemoselective reduction of the enone **(21)** would afford the *endo*-alcohol **(180)** (Scheme 4.6). Several methods were employed to effect this reduction. The first method utilised was the well-known Luche reduction[124] which utilises the Lewis-acid cerium trichloride as a means of potentiating the enone **(21)** for nucleophilic reduction by sodium borohydride, which is considered a mild and selective reducing agent.[125] In our hands, attempts at utilizing a large excess of the Lewis-acid still only yielded several products, one of which has been identified as **179** resulting from exhaustive reduction of the α, β-unsaturated system.



Scheme 4.6 *Reagents and conditions:* (i) $NaBH_4$, $CeCl_3.7H_2O$ (1eq), MeOH, rt to reflux (ii) $NaBH_4$, $CeCl_3.7H_2O$ (2eq), MeOH, rt to reflux (iii) DIBAL-H, toluene, -78°C, 20 min, 77% (iv) $VO(acac)_2$, *t*-BuOOH , toluene, rt to reflux, *m*-cpba, $CHCl_3$, reflux, 3 h.

A survey of the literature revealed that Ogasawara *et al* [126] had successfully utilized DIBAL-H to effect the above chemical transformation. Chemoselective reduction of the enone **(21)** rendered the required *endo*-alcohol **(180)** in a yield of 77%. Spectroscopic and analytical evidence confirmed the structure of **180** and the presence of the *endo* alcohol. Spectroscopic data were consistent with the assigned structure. Elucidation of the ^1H NMR spectrum revealed the appearance of a new signal at δ 4.67 could be attributed to H-3. A comparison with the *exo*-alcohol **(78)** indicated a downfield shift of H-3 which resonates at δ 4.07 in this species. Further confirmation was acquired from the characteristic IR OH stretching frequency at 3599.

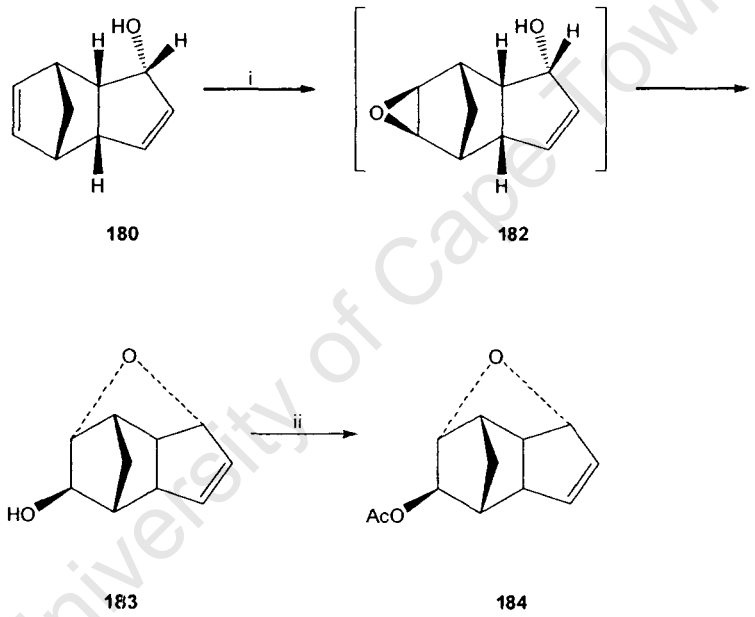
Table 4.1 NMR data of **78** and **185**

Proton	*Exo* alcohol 78	*Endo* alcohol 180	Carbon	Exo alcohol 78	Endo Alcohol 180
H-1	3.36 (m)	2.89-2.98 (m)	C-1	44.9*	46.9
H-2	3.04 (m)	3.29 (dd, *J* 7.2 and 3.9 Hz)	C-2	54.8*	54.0
H-3	4.07 (m)	4.67 (br d, *J* 8.1 Hz)	C-3	79.2	75.9
H-4	5.93 (dd, *J* 5.8 and 3.2 Hz)	6.15 (dd, *J* 5.7 and 2.4 Hz)	C-4	135.4	135.2
H-5	5.60 (br d, *J* 6.0 Hz)	5.81 (dd, *J* 5.6 and 3.2 Hz)	C-5	138.0	135.2
H-6	2.53 (m)	2.89-2.98 (m)	C-6	53.7*	52.5
H-7	2.8 (m)	2.89-2.98 (m)	C-7	51.4*	47.0
H-8	5.77 (br d, *J* 5.6 Hz) or 5.84 (dd, *J* 5.6 and 3.2 Hz)	5.59 (2H, m)	C-8	134.8	134.6
H-9	5.77 (br d, *J* 5.6 Hz) or 5.84 (dd, *J* 5.6 and 3.2 Hz)	5.59 (2H, m)	C-9	132.4	133.4
H-10	1.37 (br d, *J* 8.12 Hz) and 1.55 (br d, *J* 8.12 Hz)	1.48 (br d, *J* 8.4 Hz) and 1,57 (dt, *J* 2 x 8.4 and 1.8 Hz)	C-10	44.8	44.7

* Not unambiguously assigned

Attempts at formation of the epoxide using $VO(acac)_2$, yielded only starting enone **(21)**, presumably *via* oxidation of the allylic alcohol by *t*-butylhydroperoxide. The use of *m*-cpba rendered the product which was identified as **183**. Although initial analysis of the spectroscopic data was

thought to indicate the presence of the epoxide **181**, attempts at opening of the epoxide using both lithium aluminium hydride and the grignard reagent ethyl magnesium bromide did not validate this. Further analysis of the data led to the conclusion that **183** had formed rather than the expected epoxide. Formation of **183** must occur *via* the intermediate epoxy-alcohol **(182)** which undergoes an intramolecular opening *via* nucleophilic attack by the free hydroxyl group (Scheme 4.7). The alcohol of the cyclic ether **(183)** was acetylated as a means of further validation to yield **184**. Disappearance of the signal corresponding to the hydroxy proton in the ^{1}H NMR provided further evidence of it's presence in **183**.

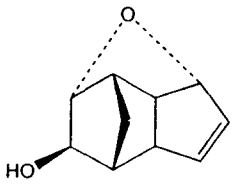


Scheme 4.7 *Reagents and conditions:* (i) *m*-cpba, $CHCl_3$, reflux, 3 h,77% (ii) Ac_2O, DMAP (cat), pyridine, rt, 20 h, 49%.

The proton NMR was fully assigned with the aid of the COSY spectrum (Figure 4.2). The characteristic proton for H-3 resonates at δ 4.66 as a doublet of

doublets (*J* 5.2 and 1.8 Hz). This is confirmed by a cross peak in the COSY from H-4 which is the only olefinic proton with coupling to a proton on an oxygen-bearing proton. Hence H-4 is assigned as the most deshielded proton resonating at δ 5.91 (*J* 5.2 and 1.8 Hz) with a large coupling to H-5 (δ 5.75, br dd, *J* 5.2 and 2.0). A cross peak from H-3 allowed for allocation of H-2 which resonates as a multiplet at δ 2.99 and a small "W" coupling of H-3 to H-6 is also observed. The position of H-6 is confirmed by the cross peak from H-5 which reveals H-6 as a multiplet at δ 2.90. H-2 is expected to couple to H-1 and hence H-1 can be located from its cross peak. H-1 resonates at δ 2.69. A cross peak from H-6 reveals the location of the distinctly shielded H-7 resonating at δ 2.13 and further verifies the position of H-2 *via* long range coupling. H-8 and H-9 were unambiguously assigned. The H-8 proton was located using the COSY spectrum as a cross peak from H-7 (δ 2.13) and resonates at δ 3.88 in the ^{1}H NMR spectrum. As a result of the dihedral angle of approximately 90° between H-8 and H-9, the COSY spectrum shows no cross coupling peaks between these two protons. However, H-9 can be assigned on the basis of it being the only other olefinic proton (δ 4.07) as well as its coupling to H-1 (δ, *J* 4.4). The protons for H-10 could also be assigned and were shown to resonate as doublets at δ 2.23 (*J* 10.4 Hz) and δ 1.82 (*J* 10.4 Hz). These are allocated as a cross peak from H-1 which is shown to couple to both H-10_a and H-10_b. H-8 reveals a long range coupling to either H-10_a or H-10_b.

Assignment of the ^{13}C NMR spectrum was verified using HSQC experiments. These couplings have been illustrated in Figure 4.3. High resolution MS results proposed a molecular ion with M^+ 164.0141. The proposed structure has been unequivocally confirmed by crystal structure analysis (Figure 4.4).



183

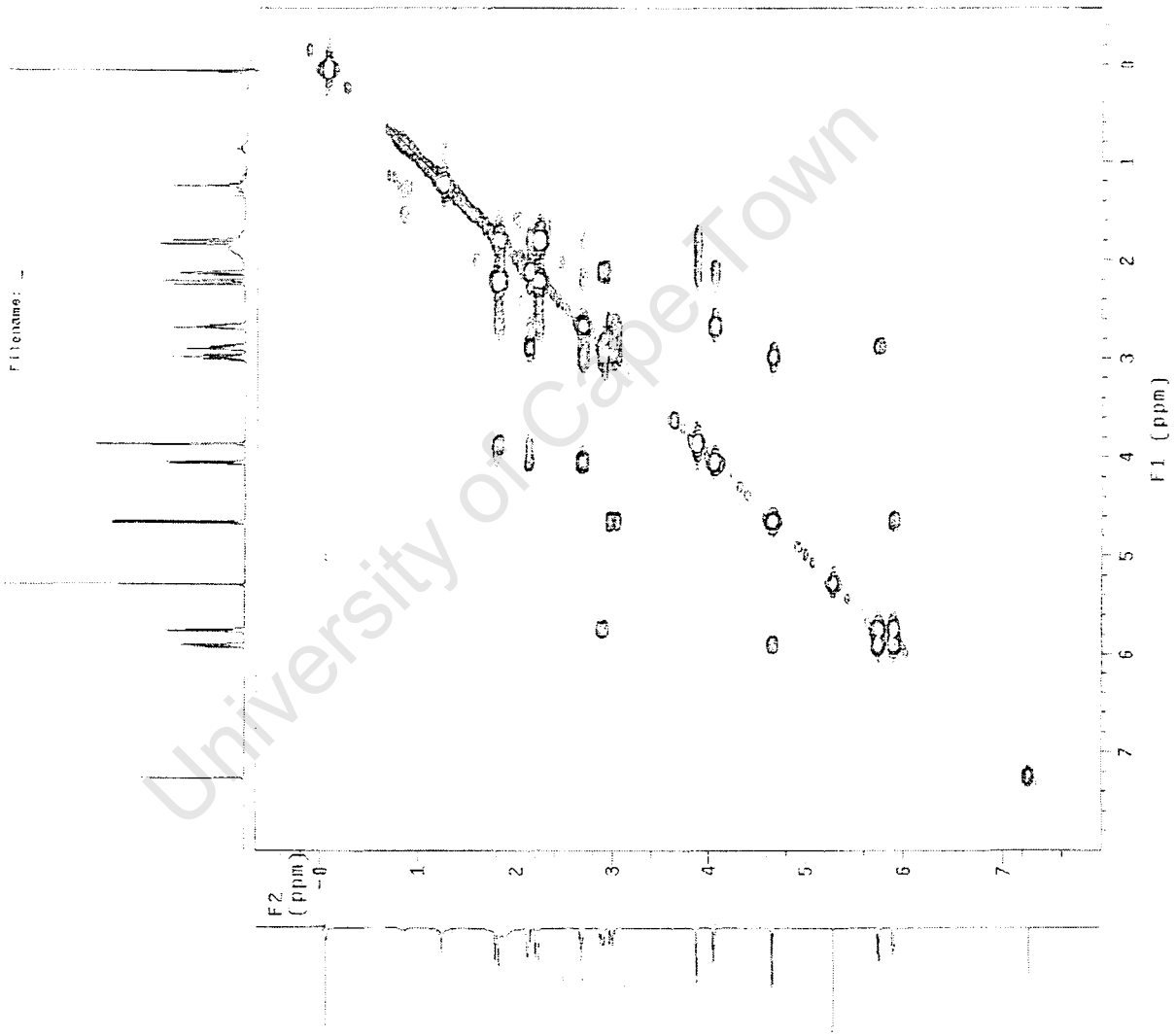


Figure 4.2 Cosy spectrum of **183**.

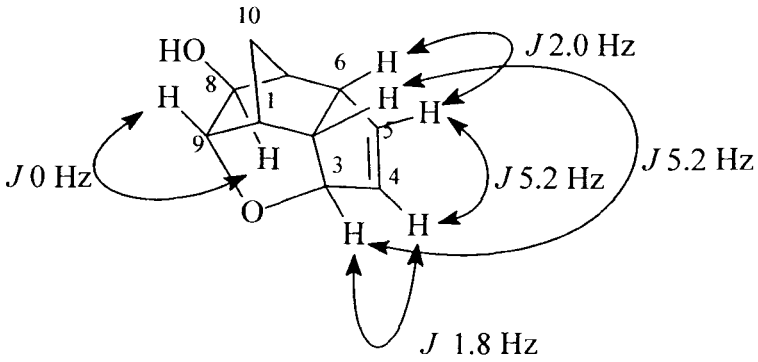


Figure 4.3 Selected coupling constants for **183** (*J* values in Hz).

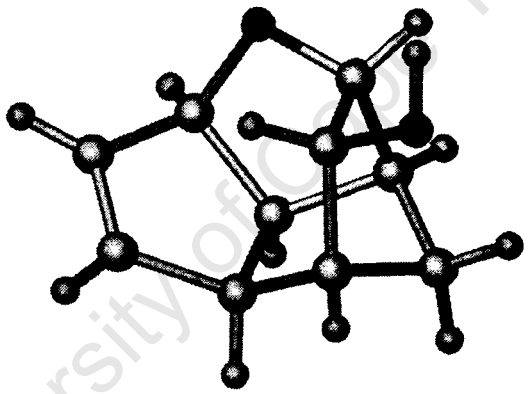
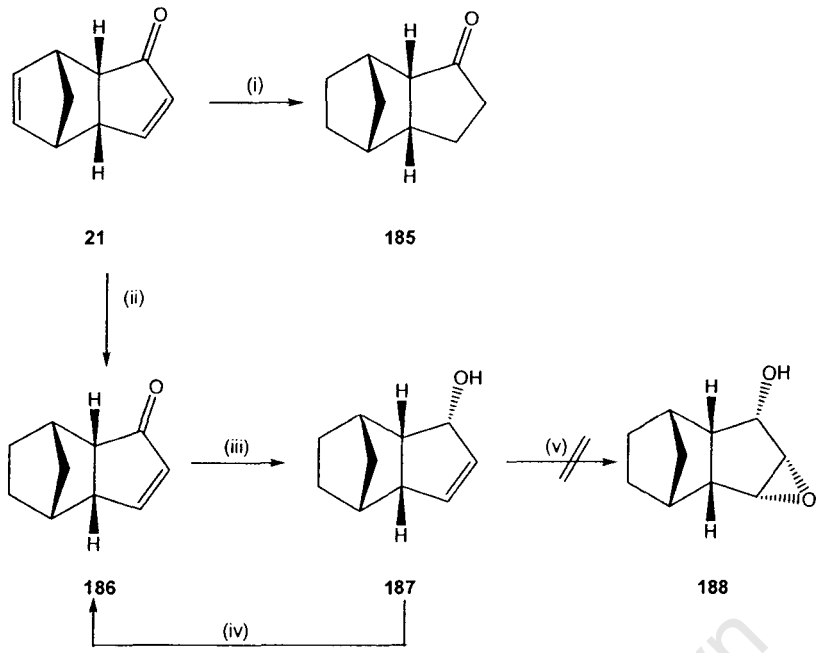


Figure 4.4 Crystal structure of **183**.

Following this, an alternative approach was attempted. This involved chemoselective reduction of the C8/C9 double bond of the enone **(21)** without reducing the α,β-unsaturated system (Scheme 4.8). Thus **(21)** was hydrogenated at atmospheric pressure in the presence of palladium on carbon for 18 h. This led to the reduction of both double bonds as in **185** which was

verified by the complete disappearance of all olefinic signals in the ^{1}H and ^{13}C NMR spectra. Reducing the time of the reaction to 1 h afforded the target **186**. The chemoselective reduction has been verified by the presence of the much deshielded H-4 proton, (ddd, δ 7.57), in the ^{1}H NMR spectrum. C-4 is clearly present in the ^{13}C NMR spectrum resonating at a similar position to where it was located in the **21** ^{13}C spectrum, δ 162.7. The HRMS results proposed a parent molecular ion with M^{+} 148.0868. All of these data confirm the above structure. Diisobutylaluminium hydride (DIBAL-H) reduction yielded the *endo*-alcohol **(187)**. The ^{1}H NMR spectrum of the product carried a signal implying the presence of the hydroxyl moiety (doublet, δ 4.88). The ^{13}C NMR spectral interpretation verified this hydroxyl group with C-3 resonating at δ 76.5. Rationalisation of the stereochemistry of the product lies in the sterically congested *endo*-face of the molecule which directs the reducing agent to the *exo*-face resulting in formation of the proposed *endo*-alcohol. Attempted $VO(acac)_2$ mediated epoxidation afforded **188** while *m*-cpba mediated epoxidation rendered an as yet unidentifiable species.



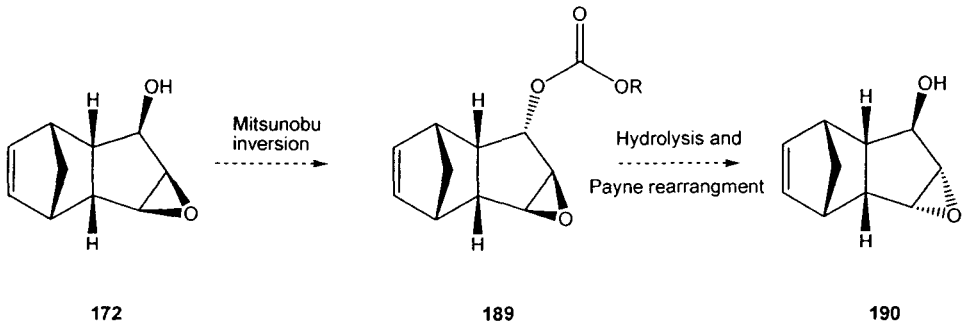
Scheme 4.7: (i) Pd/C, H_2, rt, 20 h, 80% (ii) Pd/C, H_2, rt, 1 h, 64% (iii) DIBAL-H, toluene, -78°C, 20 min, 80%(iv) *m*-cpba, CH_2Cl_2, (v) $VO(acac)_2$, toluene, reflux.

Payne rearrangement

The next method that was attempted for formation of the *endo*-epoxide involved performing a Mitsunobu inversion of the *exo*-epoxyalcohol **(172)** to generate the *exo*-epoxy-*endo*-ester **(189)** which, after hydrolysis, was expected to undergo a Payne rearrangement to give the *endo*-epoxy-*exo*-alcohol **(190)** (Scheme 4.9). Facile opening of the epoxide would then be expected on the basis of *exo*-approach of the incoming nucleophile.

The secondary alcohol **(172)** was subjected to an enhanced Mitsunobu reaction in which **172** was treated with DIAD in the presence of triphenylphosphine and *p*-nitrobenzoic acid as nucleophile (Scheme 4.10). Historically the use the activated carboxylic acid, *p*-nitribenzoic acid, as opposed to benzoic acid has been shown to increase the efficiency of the reaction threefold. [127]While Zibari *et al*[128] reported higher yields of the inverted

product using benzene rather than THF as solvent, in our hands, the use of THF produced perfectly acceptable yields.

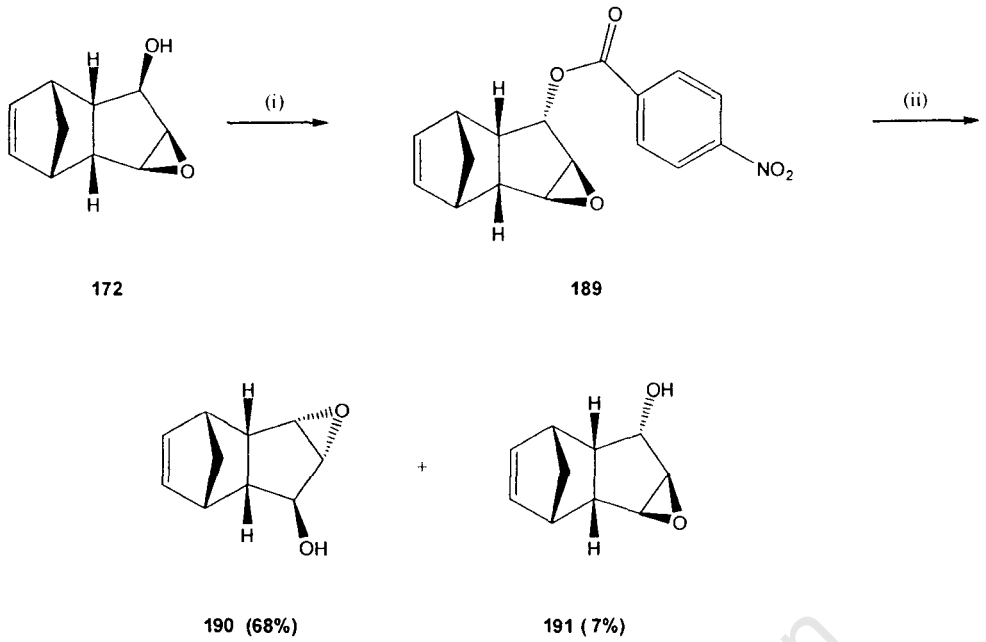


172 189 190

Scheme 4.9 Proposed synthetic plan for the synthesis of the *endo*-epoxy alcohol **(190)**.

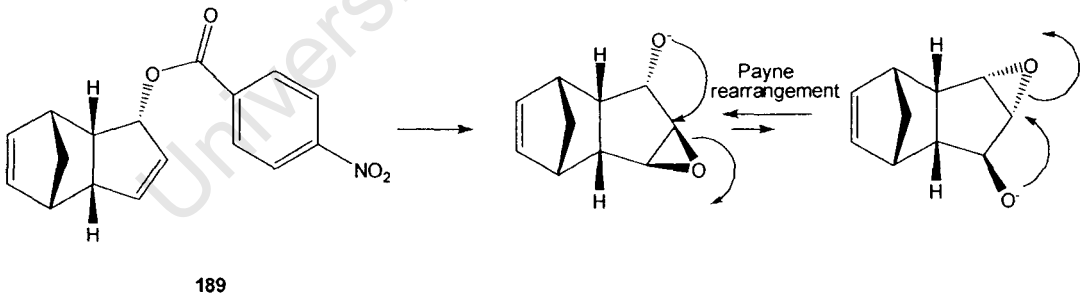
The ^{1}H NMR of the epoxy ester **(189)** indicates a downfield shift (δ 5.64) of H-3 relative to its position in the epoxy alcohol **(172)** (δ 3.79). H-3 resonates as a ddd (*J* 5.3, 4.4 and 0.6 Hz) with couplings to H-2, H-4 and "W"-coupling to H-6. The signal is much less diagnostic in **172** resonating as a broad singlet. A key signal in ascertaining whether inversion of the alcohol had indeed taken place, is H-2. H-2 resonates at δ 2.61 (dddd, *J* 10.2, 4.4, 1.2 and 1.0 Hz). These couplings can be assigned to the interaction of H-2 with H-3, which would produce the large coupling, H-6 and H-1. The smallest coupling constant can be attributed to its interaction with H-7 in which we see a long range "W" coupling. Considering model structures, it is clear that this coupling could not have occurred if H-2 was *endo*. Hence, we can conclude that the *endo*-ester has been generated. Subsequent chemical transformation of **189** supported this assignment.

Thus, the epoxy-ester **(189)** was then hydrolysed with potassium carbonate in methanol and underwent the Payne rearrangement (Scheme 4.10).



Scheme 4.10 *Reagents and conditions*: (i) DIAD, PPh_3, *p*-nitrobenzoic acid, THF, 60°C, 4 h, 81%; (ii) K_2CO_3, MeOH, 25°C, 4 h.

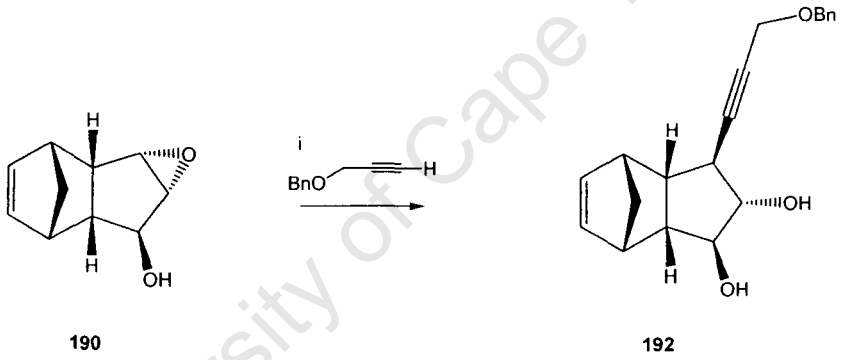
Nucleophilic opening of the epoxide by the oxygen anion is a reversible process with the thermodynamic equilibrium favouring formation of the *endo*-epoxide-*exo*-alcohol (Scheme 4.11).



Scheme 4.11 Thermodynamic equilibration of the payne rearrangement.

The presence of the assigned structures of **190** and **191** were confirmed by NMR with the minor product being assigned as the one in which the hydroxyl group is *endo*. The signal attributed to H-3 was exploited in this assignment. H-3 resonates as at δ 4.86 (dd, *J* 6.8 and 2.8 Hz) in **190** while it is found at δ 4.87 (ddd, *J* 6.6, 2.8 and 0.6 Hz) in **191**. H-3 has an extra coupling in **191** which is attributed to the "W" coupling to H-6. This coupling is only possible in the example in which H-3 is *endo*. Hence, **191** is assigned as the *exo*-alcohol which is the minor product obtained in only 7 % yield.

Direct comparison with the opening of the *exo*-epoxide-*exo*-alcohol **(172)** was made by treating **190** with the anion derived from alkyne (Scheme 4.12), used in the opening of the *exo*-epoxide in Scheme 4.4. The good yield obtained relative to one obtained with the *exo*-epoxide **(172)** opening serves as further confirmation for the formation of the *endo*-epoxide.



190 **192**

Scheme 4.12 *Reagents and conditions*: (i) *n*-BuLi, THF, 78°C, 6 h, 66 %.

The regioselectivity of the nucleophilic opening was assigned by inspection of the H-5 proton which resonates at δ 2.78 (dd, *J* 9.1 and 8.4 Hz), diagnostic for a proton α to a triple bond. Furthermore, if generation of the opposite regioisomer had occurred, the proton adjacent to the alkyne group would be seen to couple to both of the protons adjacent to the two hydroxyl bearing carbons. The *exo* approach of the nucleophile is confirmed by the *trans*-

relationship between H-4 and H-5 which is revealed by the large coupling constant of 9.1 Hz between the two. This is indicative of a H4-H5 dihedral angle approaching 180°.

4.2 Conclusion

With the *endo* epoxide synthesis in place and facile opening thereof established, this creates a platform for elaboration to produce the requisite oxygen analogue targets. The system is now well set up for extension as indicated in Figure 4.2. It allows for variation of the nucleophiles installed for evaluation of the biological properties thereof.

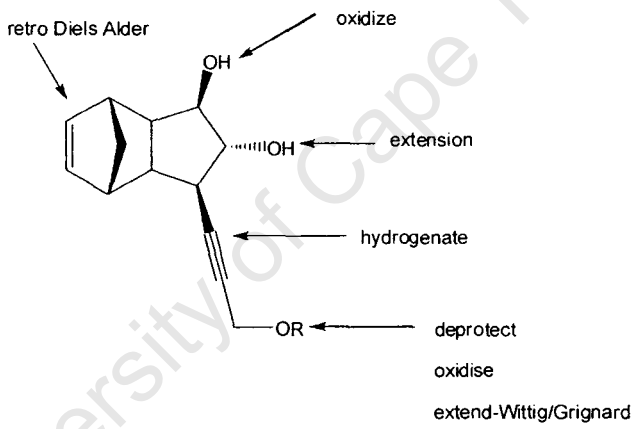


Figure 4.5 Points of elaboration for formation of oxygen analogues of PG's.

It is envisaged that **173** may be converted to enantiopure enone *via* an enzyme-mediated desymmetrisation. This would allow for asymmetric synthesis of the envisaged analogues.

CHAPTER 5

EXPERIMENTAL

General:

Melting points were determined on a Reichert-Jung Thermovar and a Fischer-Johns hot stage microscope and are uncorrected. Proton nuclear magnetic resonance spectra were recorded using trimethylsilane as an internal standard on a Varian VXR-200 (200MHz), Varian Mercury (300MHz) or a Varian Unity Spectrometer (400MHz). Carbon –13 nuclear magnetic resonance spectra were determined on the same instruments at 50, 75 or 100MHz (using trimethylsilane as an internal standard). Infrared spectra were recorded in solutions specified using a Perkin Elmer Paragon 1000 FT-IR spectrometer. Elemental analyses were performed using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70eV with an accelerating voltage of 4kV. Accurate masses were determined using a VG-70E spectrometer at the University of the Witwatersrand.

All reactions were monitored by thin layer chromatography using aluminium-backed silica gel $60F_{254}$ plates (Merck). The plates were visualised by a combination of ultraviolet light (254nm) and either anisaldehyde spray [prepared from a 2.5% solution of *p*-methoxybenzaldehyde ($20cm^3$) and 18 M sulphuric acid ($1\ cm^3$)] or cerium (IV) ammonium sulfate in 8 M sulphuric acid and baking at 200°C. Column chromatography was carried out on silica gel (Merck Kieselgel 60: 70-230 mesh for gravity and 230-400 mesh for flash chromatography).

All solvents used were dried by the appropriate technique.[129] Tetrahydrofuran and diethyl ether were dried over sodium wire prior to use using benzophenone

as indicator. Triethylamine was dried over and distilled from calcium hydride and it was stored over potassium hydroxide pellets. Dichloromethane was dried over phosphorous pentoxide and distilled. Solvents not mentioned which were used in reactions were anhydrous unless stated otherwise.

exo-3-Acetoxytricyclo[5.2.1.0$^{2.6}$]-deca-4, 8-diene (77)

Acetic anhydride (61 cm^3) was added to a solution of manganese (III) acetate (40 g, 165 mmol) in acetic acid added (160 cm^3) and the mixture was refluxed for 20 minutes. Potassium permanganate (6.5 g, 40.9 mmol) was added portion wise to this hot solution and the mixture was then refluxed for a further 30 minutes. After cooling to 70°C, dicyclopentadiene (19.6 cm^3, 146 mmol) was added followed by potassium bromide (2.95 g, 24.8 mmol) and the reaction mixture stirred at that temperature until the dark colour of the manganese (IV) ion had faded (~2 h). After cooling, the solution was filtered through a Celite pad, diluted with water and extracted with ethyl acetate (3 x 75 cm^3). The organic extract was washed successively with saturated $NaHCO_3$, H_2O and brine, dried over magnesium sulfate and evaporated under reduced pressure. Column chromatography on a silica gel column using ethyl acetate-hexane (1:9) afforded the *acetate* **77**(14 g, 50%) as colourless oil; δ_H (200 MHz, $CDCl_3$): 1.39 (1H, d, *J* 8.2 Hz, H-10$_a$), 1.58 (1H, d, *J* 8.2 Hz, H-10$_b$), 2.02 (3H, s, C*H*$_3$), 2.59 (1H, m, H-7), 2.82 (1H, br m, H-6), 3.1 (1H, br m, H-2), 3.40 (1H, m, H-1), 4.90 (1H, m, H-3), 5.60 (1H, dd, *J* 5.6 and 2.8 Hz, H-8), 5.89-5.83 (2H, m, H-5 and H-9) and 6.02 (1H, dd, *J* 5.6 and 2.8 Hz, H-4).

exo-3-Hydroxydicyclopentadiene (78)

The acetate **77** (14 g, 74 mmol) in was stirred with potassium carbonate (32 g, 368.5 mmol) in methanol (125 cm^3) at 24°C for 18 h. The mixture was filtered

through a Celite pad and washed with methanol (3 x 75 cm^3) and the methanol removed under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic product extracted into ethyl acetate (3 x 75 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel using ethyl acate-petroleum ether (3:7) afforded the *alcohol* **78** (9.3g, 85%) as a crystalline solid; m.p. 72-73°C (from hexane) (lit 71.5-72 °C); ν_{max}/cm^{-1} 3430 (OH); δ_H (400 MHz, $CDCl_3$) 1.37 (1H, br d, *J* 8.1 Hz, H-10_a or H-10_b), 1.55 (1H, br d, *J* 8.1 Hz, H-10_a or H-10_b), 2.53 (1H, m, H-6), 2.8 (1H, m, H-7), 3.04 (1H, m, H-2), 3.36 (1H, m, H-1), 4.07 (1H, m, H-3), 5.60 (1H, br d, *J* 6.0 Hz, H-5), 5.77 (1H, br d, *J* 5.6 Hz, H-8 or H-9), 5.84 (1H, dd, *J* 5.6 and 3.2 Hz, H-8 or H-9) and 5.93 (1H, dd, *J* 5.8 and 3.2 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 44.8 (C-10), 44.9, 51.4, 53.7, 54.8, 79.2 (C-3), 132.5, 134.8, 135.5 and 138.0; (Found M^+ 148.0889; $C_{10}H_{12}O$ requires 148.0888).

Synthesis of Pyridinium Chlorochromate (PCC) on alumina

To a solution of chromium trioxide (8.4 g, 84.45 mmol) and 6N HCl (14.1 cm^3), pyridine (6.7 g, 85.45 mmol) was added at 40°C within 10 minutes. The mixture was then kept at 10°C for 30 minutes resulting in the formation of a yellow-orange solid. Reheating to 40°C yielded a solution to which alumina (70 g) was added. After evaporation under reduced pressure, the orange solid was dried under vacuum for 2 h at 24°C.

3-Oxodicyclopentadiene (21)

PCC supported on alumina (84.45 mmol) was added to a flask containing a solution of the alcohol **78** (5 g, 33.8 mmol) in *n*-hexane (80 cm^3). The mixture was stirred at 24° for 18 h. The solid was filtered through a Celite pad and washed with diethyl ether (3 x 75 cm^3). The combined filtrate was dried over

magnesium sulfate and evaporated. Column chromatography on silica gel using ethyl acetate-petroleum ether, (3:7) yielded the *ketone* **21** (4.7g, 96%) as a white crystalline solid; m.p. 74-75°C (from hexane) (lit 76°C); $^{130}\nu_{max}/cm^{-1}$ 1693 cm^{-1} (Found: C, 82.1; H, 6.9; $C_{10}H_{10}O$ requires C, 82.3; H, 6.8); δ_H (300 MHz, $CDCl_3$): 1.62 (1H, d, *J* 8.6 Hz, H-10_a or H-10_b), 1.74 (1H, d, *J* 8.6 Hz, H-10_a or H-10_b), 2.78 (1H, m, H-6), 2.96 (1H, m, H-2), 3.22 (1H, m, H-7), 3.41 (1H, m, H-1), 5.77 (1H, dd, *J* 5.5 and 2.8 Hz, H-4), 5.95-5.91 (2H, m, H-8 and H-9) and 7.36 (1H, dd, *J* 5.5 and 2.4 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 44.3, 45.2, 48.5, 50.4, 52.9 (C-1, C-2, C-6, C-7, C-10), 132.5 (C-8), 132.8 (C-9), 137.2 (C-4), 164.6 (C-5) and 210.6 (CO).

exo-5-_n_ Butyl-tricyclo[5.2.1.$0^{2.6}$]-dec-8-ene-3-one (82)

n-Butyl lithium (1.6 M in hexane, 6.3 cm^3) was added gradually to a suspension of copper iodide (1.4 g, 7.4 mmol) in dry ether (10 cm^3) at 0°C. The mixture was stirred at this temperature for 15 minutes. The ketone **(21)** (375 mg, 2.6 mmol) in dry ether (10 cm^3) was added gradually to the reaction vessel and the solution was allowed to warm to 24°C. The mixture was stirred at 24°C for 2 h. Saturated aqueous ammonium chloride was added and the aqueous phase extracted with ether (2 x 50 cm^3). The combined organic extracts were washed with water, dried over magnesium sulfate and the solvent evaporated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) yielded the *alkyl ketone* **(82)** (327 mg, 62%) as a clear oil; ν_{max}/ cm^{-1} 1734 (CO); (Found: M^+, 204.1517. $C_{14}H_{20}O$ requires 204.1514); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8 Hz, *CH_3*), 1.25-1.43 (7H, m, 3 x *CH_2* and H-10_a or H-10_b), 1.54 (1H, br d, *J* 4.4 Hz, H-10_a or H-10_b), 1.68 (1H, m, H-5), 1.93 (1H, ddd, *J* 18.4 , 6.8 and 2.0 Hz, H-4_{exo}), 2.20 (1H, dd, *J* 18.4 and 7.8 Hz, H-4_{endo}),), 2.64 (1H, dt, *J* 2 x 9.4 and 4.2 Hz, H-6), 2.92 (1H, ddd, *J* 9.4, 4.8 and 2.0 Hz, H-2), 3.01 (1H, m, H-7), 3.16 (1H, m, H-1) and 6.13 (2H, m, H-8 and H-

9); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 36.8 (C-5), 37.5 (CH_2), 6.1 (C-1), 47.1 (C-7), 48.3 (C-4), 48.75 (C-6), 52.3 (C-10), 54.8 (C-2), 135.2 (C-8), 136.1 (C-9) and 220.9 (CO).

5-*n*-Butyl-4-methyl-tricyclo[5.2.1.$0^{2,6}$]-deca-8-ene-3-one (86)

1. *n*-Butyllithium (2.5M in hexane, 0.43 cm^3) was added to a stirred solution of diisopropylamine (0.15 cm^3, 1.18 mmol) in dry tetrahydrofuran (8 cm^3) at -78°C under nitrogen. The resulting solution was warmed to 0°C and stirred for 30 min. The solution was cooled to -78°C and a solution of **82** (200 mg, 0.98 mmol) in tetrahydrofuran (4 cm^3) was added. After stirring at this temperature for 30 min tributyltin(I) chloride was added and stirring was continued for a further 30 min. Hexamethlphosphorotriamide (0.44 cm^3, 2.5 mmol) and iodomethane (0.18 cm^3, 2.94 mmol) were added consecutively and the reaction was stirred for another 30 min at -78°C, then warmed to ambient temperature and stirred for 23 h. The mixture was diluted with saturated aqueous ammonium chloride and extracted with diethyl ether (3 x 20 cm^3). The organic extract was washed consecutively with water and sodium thiosulfate, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) as eluent yielded **86** (132 mg, 62%); ν_{max}/cm^{-1} 1716 (CO); δ_H (300 MHz, $CDCl_3$) 0.92 (6H, t, *J* 7.2 Hz, 2 x C*H*$_3$), 1.28-1.64 (9H, m, H-5, 2 x H-10, 3 x C*H*$_2$), 2.19 (1H, m, H-4), 2.58 (1H, quintet, *J* 9.9 and 4.6 Hz, H-6), 2.98 (2H, m, H-2, H-7), 3.15 (1H, m, H-1) and 6.14 (2H, m, H-8, H-9); δ_C (100 MHz, $CDCl_3$) 11.4 (CH_3), 14.3 (CH_3), 23.2 (C-10), 30.0 (CH_2), 31.4 (CH_2), 40.3 (CH_2), 46.1 (C-5), 46.5, 47.1, 50.5, 52.9 (C-1, C-6, C-7, C-2), 53.4 (C-4), 135.6 (C-8 or C-9) and 136.4 (C-8 or C-9); (Found M^+-C_5H_6 152.1218 $C_{15}H_{22}O$ requires 218.1617) followed by **82** (45 mg, 23%).

2. *n*-Butyl lithium (2.5 M in hexane, 0.68 cm^3) was added to a suspension of copper iodide (160 mg, 0.85 mmol) in dry tetrahydrofuran (4 cm^3) at -78°C. The solution was allowed to warm to -20°C and stirred for 1-2 min before being recooled to -78°C. A solution of the enone **(21)** (100 mg, 0.68 mmol) in dry tetrahydrofuran (2 cm^3) was added and the reaction srirred at -78°C for 30 min. Addition of hexamethylphosphorictriamide (0.50 cm^3) and iodomethane (0.20 cm^3, 3.2 mmol) was followed by stirring at the same temperature for 30 min and then allowing the reaction to warm to 24°C. The reaction was quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (1 x 30 cm^3, 2 x 10 cm^3), dried over sodium sulfate and concentrated under reduced pressure. The crude material (135 mg) was chromatographed on silica gel using ethyl acetate-petroleum ether (3:97) to yield **86** (99 mg, 67%); ν_{max}/cm^{-1} 1716.(CO); δ_H (400 MHz, $CDCl_3$) 0.92 (6H, m, 2 x C*H*$_3$), 1.19-1.44 (7H, m, H-10_a, 3 x C*H*$_2$), 1.56 (1H, dt, *J* 2 x 8.0 and 1.8 Hz, H-5), 1.67 (1H, m, H-10_b), 2.19 (1H, quintet, *J* 15.6 and 7.8 Hz, H-4), 2.58 (1H, quintet, *J* 10.0 and 4.7 Hz, H-6), 2.98 (2H, m, H-2, H-7), 3.15 (1H, m, H-1) and 6.14 (2H, ddd, *J* 14, 5.6 and 3.2 Hz, H-8, H-9); δ_C (100 MHz, $CDCl_3$) 11.4 (CH_3), 14.3 (CH_3), 23.2 (C-10), 30.0 (CH_2), 31.4 (CH_2), 40.3 (CH_2), 46.1 (C-5), 46.5, 47.1, 50.5, 52.9 (C-1, C-6, C-7, C-2), 53.4 (C-4), 135.6 (C-8 or C-9) and 136.4 (C-8 or C-9); (Found M^+-C_5H_6 152.1218 $C_{15}H_{22}O$ requires 218.1617) the 1,2 addition product **(116)** (41 mg, 39%); ν_{max}/cm^{-1} 3590.0 (OH); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, m, C*H*$_3$), 1.31-1.37 (6H, m, 3 x C*H*$_2$), 1.44 (1H, br d, *J* 7.6 Hz, H-10_a), 1.53-1.59 (1H, m, H-10_b), 2.61 (1H, dd, *J* 8 and 4.2 Hz, H-6), 2.89 (2H, m, H-2, H-7), 3.26 (1H, m, H-1), 5.47 (2H, ddd, *J* 22.5, 5.6 and 1.7 Hz, H-4, H-5), 5.85 (1H, dd, *J* 5.7 and 3.2 Hz, H-8 or H-9) and 6.17 (1H, dd, *J* 5.7 and 3.2 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 23.4 (C-10), 26.1 (CH_2), 43.2 (CH_2), 45.5 (CH_2),

46.9, 52.7, 53.6, 53.8 (C-1, C-2, C-6, C-7), 83.8 (C-3), 133.35 C-4 or C-5), 134.1(C-4 or C-5), 135.27 (C-8 or C-9) and 138.6 (C-8 or C-9); (Found M^+ 204.1518 $C_{14}H_{20}O$ requires 204.1514).

5-(Tetrahydro-2′-pyranyloxy)-1-iodo-pentane (87)

1) Iodine (2.0 g, 16 mmol) was added to a stirred solution of the mono-THP protected alcohol **(101)** (1.0 g, 5.3 mmol), imidazole (1.1 g, 16 mmol) and triphenylphosphine (4.2 g, 16 mmol) dissolved in ether: acetonitrile (1:3, 60 cm^3). The mixture was stirred at 24°C for 3.5 h and the solvent was then removed under reduced pressure. Column chromatography gave the iodinated product **87** (0.134 mg, 67%) as pale orange oil; ν_{max}/cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.46-1.89 (12H, m, 6 x CH_2), 3.20 (2H, t, *J* 7.0 Hz, H-1), 3.39 (H, dt *J* 2 x 9.5 and 6.3 Hz, H-5), 3.50 (H, m, H-6′), 3.75 (H, dt, *J* 2 x 9.5 and 6.7 Hz, H-5), 3.86 (H, m, H-6′) and 4.57 (H, dd, *J* 4.4 and 2.8 Hz, H-2′); δ_C(100 MHz, $CDCl_3$) 7.0 (C-1), 19.9, 25.7, 27.5, 28.9, 31.0, 33.6 (C-3′-C-5′ and C-2-C-4), 67.4, 62.6 and 99.1 (C-6′, C-5, C-2′); (Found M^+ 298.0441 $C_{10}H_{19}IO_2$ requires 298.0430).

2) Sodium iodide (1.97 g, 13.1 mmol) was added to a solution of **102** (2.97 g, 10.1 mmol) in acetone (50 cm^3). The mixture was refluxed for 21 h. The reaction was quenched by adding water and the crude organic product was extracted into ethyl acetate (3 x 20 cm^3). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. Column chromatography of the residue on silica gel with ethyl acetate-petroleum ether (1:9) as eluent gave adduct **87** (1.50 g, 50%); ν_{max}/cm^{-1}; ; δ_H(400 MHz, $CDCl_3$) 1.46-1.89 (12H, m, 6 x CH_2), 3.20 (2H, t, *J* 7.0 Hz, CH_2-I), 3.39 (H, dt *J*

9.5 and 2 x 6.3 Hz, H-5), 3.50 (H, m, H-6'), 3.75 (H, dt, *J* 2 x 9.5 and 6.7 Hz, H-5), 3.86 (H, m, H-6') and 4.57 (H, dd, *J* 4.4 and 2.8 Hz, H-2'); δ_C(100 MHz, $CDCl_3$) 7.0 (CH_2-I), 19.9, 25.7, 27.5, 28.9, 31.0, 33.6 (C-3'-C-5' and C-2-C-4), 67.4, 62.6 and 99.1 (C-6', C-5, C-2'); (Found M^+ 298.0441 $C_{10}H_{19}IO_2$ requires 298.0430).

exo-5-Ethyl- -tricyclo-[5.2.1.$0^{2,6}$]-dec-8-en-3-one (88)

Bromoethane (0.3 cm^3, 4.00 mmol) was added gradually to magnesium turnings (78.3 mg, 3.22 mmol) in dry ether (10 cm^3) and the mixture was stirred until the magnesium had been consumed. To the turbid mixture was added dry CuI (20 mg, 0.11 mmol) and the resulting green-yellow mixture stirred at 0°C for 30 minutes. The mixture was cooled to - 78°C and a solution of enone (**21**) (100 mg, 0.68 mmol) in ether (10 cm^3) was added drop wise over a period of 5 min. After stirring for 1 h at - 78°C, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The aqueous phase was extracted with ether and the combined organic phase washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Column chromatography on silica-gel (10 g, ethyl acetate-hexane; 1:10) gave **88** (96.5 mg, 80%) as a colourless oil. IR 1725 cm^{-1} (C=O). (Found: M^+, 176.1201. $C_{12}H_{16}O$ requires 176.1201). δ_H (300 MHz; $CDCl_3$): 6.13 (2H, *m*, H-8 and H-9), 3.18-3.12 (1H, *m*, H-1), 3.04-2.98 (1H, *m*, H-7), 2.90 (1H, *ddd*, *J* = 9.5, 4.4, 1.8 Hz, H-2), 2.60 (1H, *dt*, *J* = 9.5, 4.0 Hz, H-6), 2.18 (1H, *dd*, *J* = 18.7, 9.5 Hz, H-4_{endo}), 1.91 (1H, *ddd*, *J* = 18.7, 6.6, 1.8 Hz H-4_{exo}), 1.66-1.56 (1H, *m*, H-5), 1.53 (1H, *d*, *J* = 8.4 Hz, H-10_a or H-10_b), 1.46-1.55 (2H, *m*, CH_2), 1.40 (1H, *d*, *J* = 8.75 Hz, H-10_a or H-10_b), 0.94-0.86 (3H, *t*, *J* = 7.32 Hz, CH_3). δ_C (75 MHz; $CDCl_3$): 11.9 (CH_3), 30.5 (CH_2), 38.5 (CH_2), 46.2 (CH), 47.2 (CH), 47.9 (CH), 48.5 (CH), 52.3 (CH), 54.9 (C-10), 135.2 (C-8 or C-9), 136.0 (C-8 or C-9), 220.9 (CO); (Found M^+ 176.1201; $C_{12}H_{16}O$ requires 176.1201).

Ethyl 6-(5- ethyl-oxotricyclo[5.2.1.$0^{2,6}$]-dec-8-en-4-yl)hexanoate (89)

n-Butyllithium (2.5 M in hexane, 0.27cm^3) was added to a solution of diisopropylamine (0.1 cm^3, 0.73 mmol) in dry tetrahydrofuran (2 cm^3) at -78°C. The reaction mixture was stirred at 0°C for 30 min, and then recooled to -78°C. A solution of **88** (100 mg, 0.52 mmol) in dry tetrahydrofuran (1 cm^3) was added and stirring continued for 15 min at this temperature. **91** (440 mg, 1.56 mmol) in dry tetrahydrofuran (1 cm^3) was then added and the reaction mixture was allowed to warm to 0°C over 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3 x 20 cm^3). The extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) as eluent and gave **89** (13 mg, 8%); δ_H (300 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.5 Hz, CH_3), 2.24 (3H, t, *J* 7.1 Hz, -OCH_2CH_3), 1.54-1.80 (12H, m, 4 x CH_2, H-4 and H-5, 2 x H-10), 2.11 (2H, -$O(CO)CH_2CH_3$), 2.49 (1H, m, H-6), 2.79 (1H, m, H-7), 2.90, (1H, m, H-1), 2.99 (1H, dd, *J* 9.9 and 3.9 Hz, H-2), 4.18 (2H, q, *J* 7.2 Hz, -$(CO)OCH_2CH_3$), 6.13 (1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9) and 6.31 (1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9); followed by **88** (48 mg, 52%); ν_{max}/cm^{-1} 1725 (CO); 0.91 (3H, t, *J* 7.2 Hz, CH_3), 1.38-1.48 (3H, m, CH_2 and H-10_a), 1.54 (1H, d *J* 8.4 Hz, H-10_b), 1.61-1.64 (1H, m, H-5), 1.89-1.96 (1H, ddd, *J* 18.6, 6.6 and 2.0 Hz, H-4_{exo}), 2.20 (1H, dd, *J* 18.6 and 9.0 Hz, H-4_{endo}), 2.61 (1H, dt, *J* 9.6 and 4.0 Hz, H-6), 2.91 (1H, ddd, *J* 9.6, 4.4 and 2.0 Hz, H-2), 3.02 (1H, m, H-7), 3.16 (1H, m, H-1), 6.12 (1H, dd, *J* 5.6 and 2.8 Hz, H-8 or H-9) and 6.15 (1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9); (Found M^+ 176.1201; $C_{12}H_{16}O$ requires 176.1201).

Ethyl-6-{[(4-methylphenyl) sulfonyl] oxy}-hexanoate (91)

p-Toluenesulfonylchloride (97.8 g, 41 mmol) in dichloromethane (20 cm^3) was added to a mixture of ethyl 6-hydroxy hexanoate **(90)** (3.0 g, 18.7 mmol) and triethylamine (7.8 cm^3, 56.1 mmol) in dry dichloromethane (10 cm^3) at 0°C. The solution was stirred at this temperature for 20 min, then at 24°C for 2 h. The reaction was quenched with 1M hydrochloric acid and the aqueous layer extracted with dichloromethane. The combined organic phase was washed with saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel with ethyl acetate-petroleum ether yielded the *tosylate* **91** (3.9 g, 66%); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.2 Hz, -CH_2CH_3-), 1.33 (2H, m, CH_2), 1.56 (2H, quintet, *J* 7.6 Hz, CH_2), 1.64 (2H, m, CH_2), 2.23 (2H, t, *J* 7.4 Hz, H-2), 2.43 (3H, s, ArCH_3), 4.00 (2H, t, *J* 6.4 Hz, H-6), 4.09 (2H, q, *J* 7.2 Hz, -CH_2CH_3-), 7.32 (2H, d, *J* 8.2 Hz, 2 x Ar-C*H*) and 7.76 (2H, d, *J* 8.2 Hz, 2 x Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (PhCH_3), 21.5 (-CH_2CH_3-), 24.2 (CH_2), 24.8 (CH_2), 28.5 (CH_2), 33.9 (C-2), 60.2 (-CH_2CH_3-), 70.2 (C-6), 127.8 (ArC), 129.7 (ArC), 133.2 (ArC), 144.6 (ArC) and 173.20 (CO).

3-*t*-Butylsilyloxy-octyn-1-yne (93)

t-Butyl dimethylsilyl chloride (3.6 g, 23.8 mmol) in dimethylformamide (20 cm^3) was added to a solution of 1-octyn-3-ol **(92)** (3 g, 23.8 mmol) and imidazole (2.4 g, 35.7 mmol) in dimethylformamide (10 cm^3) at 24°C. The solution was stirred at this temperature for 18 h. The reaction was quenched with water before being extracted into ethyl acetate (3 x 20 cm^3). The combined organic extracts were washed with water and then dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel using ethyl

acetate-petroleum ether (3:97) yielded **93** (4.5 g, 78%) as a clear oil; ν_{max}/cm^{-1} 3300 (CH), 1066.7 (SiO); δ_H (300 MHz, $CDCl_3$) 0.11 (3H, s, C*H*$_3$), 0.13 (3H, s, C*H*$_3$), 0.90 (12H, s, *t*-Bu and H-8), 1.26-1.70 (8H, m, H-4-H-7), 2.36 (H, d, *J* 2.1 Hz, H-1) and 4.33 (H, td, *J* 6.6 and 2 x 2.1 Hz, H-3); δ_C (75MHz, $CDCl_3$) –5.1 (Si-CH_3), -4.6 (Si-CH_3), 14.0 (C-8), 18.23 (CH_2), 22.6 (CH_2), 24.8 (C-1), 25.8 (*t*-Bu), 31.4 (CH_2), 38.6 (CH_2), 62.8(-*C*(CH_3)$_3$-), 71.8 (C-3) and 85.8 (C-2); (Found: M^+ 240.1914; $C_{14}H_{28}OSi$ requires 240.1909).

5-(3'-*t*-Butyldimethylsilylyoxy-1'-oct-1-enyl)-tricyclo[5.2.1.0$^{2.6}$]-deca-8-ene-3-one (94)

A reaction vessel was charged with Schwartz reagent [$Cp_2Zr(H)Cl$] (1.2 g, 4.6 mmol) in dry tetrahydrofuran (7 cm^3) under nitrogen. A solution of the octyne **(93)** in dry tetrahydrofuran (15 cm^3) was added and the reaction stirred for 30 min at 24°C. The reaction mixture was then cooled to -50°C and the cooled mixture treated with methyllithim (1.4 M in diethyl ether, 6.0 cm^3) and stirred at this temperature for 10 min. This mixture was added to copper cyanide (376 mg, 4.2 mmol) in a flame-dried vessel at -50°C and stirred for 15 min. Addition of methyllithium (1.4 M in diethyl ether, 3 cm^3) was followed by stirring at -50°C for a further 15 min. A solution of enone **(21)** (613 mg, 4.2 mmol) in dry tetrahydrofuran (10 cm^3) was added and the reaction stirred at the same temperature for a further 30 min. The solution was allowed to warm to 0°C before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into ethyl acetate (3 x 15 cm^3) and filtered through Celite before being washed with brine and dried over anhydrous magnesium sulphate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) yielded the substituted enone **(94)** (789 mg, 50%) as a clear oil; ν_{max}/cm^{-1} 3682.1 (SiO), 1669.1 (CO); δ_H (400 MHz, $CDCl_3$) 0.040 (6H, m, Si(C*H*$_3$)$_2$), 0.90 12 H, t, *J* 3.0 Hz, *t*-Bu and C*H*$_3$), 1.26-1.58 (10H, m, H-

5^4 to H-5^7, 2 x H-10), 2.09-2.18 (1H, dddd, *J* 18.0, 8.0, 6.4 and 1.8 Hz, H-4_{exo}), 2.26 (1H, ddd, *J* 18.0, 8.8 and 2.8 Hz, H-4_{endo}), 2.34 (1H, m, H-5), 2.76 (1H, m, H-6), 2.95 (1H, m, H-2), 3.07 (1H, m, H-7), 3.18 (1H, m, H-1), 4.04 (1H, dd, *J* 12.4 and 6 Hz, H-5^3), 5.37 (1H, dddd, *J* 15.2, 6.8, 2.0 and 1.0 Hz, H-5^1), 5.59 (1H, ddt, *J* 15.2, 7.2 and 2 x 1.0 Hz, H-5^2) and 6.18 (2H, s, H-8 and H-9); δ_C(100 MHz, $CDCl_3$) -4.7 ($SiCH_3$), -4.2 ($SiCH_3$), 13.9 (CH_3), 22.5 (C-10), 24.9 (CH_2), 25.8 (*t*-Bu), 31.7 (CH_2), 38.3 (CH_2), 39.5 (C-4), 45.9 (C-7), 46.24 (C-1), 47.8 (C-5), 48.8 (C-6), 54.4 (C-2), 73.3 (C-5^3), 132.7 (C-5^2), 133.5 (C-5^1), 135.1 (C-90, 136.34 (C-8) and 219.2 (CO).

Ethyl-6-oxohexanoate (95)

Oxalyl chloride (1.79 cm^3, 20.6 mmol) was added to a solution of dimethyl sulfoxide (2.9 cm^3, 41.2 mmol) in dry dichloromethane (50 cm^3) at -60°C under nitrogen and the mixture stirred for 15 min. Ethyl 6-hydroxy-hexanoate **(90)** (3.02 cm^3, 18.7 mmol) was added and stirring continued for a further 15 min before the addition of triethylamine (13 cm^3). The mixture was stirred for 15 min allowing it to warm to 24°C, then quenched with 1M HCl and the mixture extracted with dichloromethane (3 x 25 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel using ethyl acetate-heptane (3:7) gave the aldehyde **95** (2.38 g, 80%); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.68 (4H, quintet, *J* 3.6 Hz, 2 x C*H*$_2$), 2.35 (4H, dt, *J* 2 x 21.2 and 7.0 Hz, H-2 and H-5), 4.13 (2H, q, *J* 7.2 Hz, -OC*H*$_2$-); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 24.1 (CH_2), 24.3 (CH_2), 33.5 (C-2), 33.9 (C-5), 60.3 (-O-CH_2), 173.8 (CO) and 179.6 (CO); (Found M^+ 158.0887; $C_8H_{14}O_3$ requires 158.0943).

Ethyl(3*E*)-6-(4-(3't-butyldimethylsilyloxy1'-oct-1-enyl)-3-oxotricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-ylidene)hexanoate (96)

1) *n*-Butyllithium (1.6M in hexane, 0.09 cm^3) was slowly added to a stirred solution of diisopropylamine (0.020 cm^3, 0.15 mmol) in dry tetrahydrofuran (1 cm^3) at -78°C. After 30 min stirring at 0°C the mixture was then recooled to -78°C and a solution of **94** (50 mg, 0.13 mmol) in tetrahydrofuran (1.5 cm^3) was added and the resulting solution was stirred for 30 min. A solution of the aldehyde **(95)** in tetrahydrofuran (1 cm^3) was added and the mixture was stirred at ambient temperature for 48 h without effecting complete conversion of the starting enone. Saturated aqueous sodium chloride was added and the mixture was extracted with ether (2 x 10 cm^3). The organic extract was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to give a yellow oil. Chromatography on silica gel using ethyl acetate- hexane (1:19) as eluent afforded the addition product **96** (3 mg, 4%); δ_H (300 MHz, $CDCl_3$) 0.013 (6H, m, $Si(CH_3)_2$), 0.88 (12H, *t*-Bu + CH_3), 1.22-1.65 (19H, m, 7 x CH_2, CH_3, 2 x H-10), 2.04 (2H, m, H-4^2), 2.26 (2H, t, *J* 7.4 Hz, -CH_2CO_2-), 2.57 (1H, m, H-5), 2.99 (2H, m, H-2 and H-6), 3.10 (1H, m, H-1), 3.25 (1H, m H-7), 4.03 (1H, dd, *J* 12.1 and 6.2 Hz, H-5^3), 4.12 (2H, q, *J* 7.1 Hz, -$CO_2CH_2CH_3$-), 5.23-5.36 (1H, H-5^2), 5.45-5.55 (1H, H-5^1), 6.01 (2H, m, H-8 and H-9) and 6.39 (1H, m, H-4^1); (Found M^+ 528.3672; $C_{32}H_{52}O_4Si$ requires 528.3635). (Found M^+ 528.3672; $C_{32}H_{52}O_4Si$ requires 528.3635).

2) A reaction vessel was charged with Schwartz reagent [$Cp_2Zr(H)Cl$] (600 mg, 2.3 mmol) in dry tetrahydrofuran (5 cm^3) under nitrogen. A solution of the octyne **93** (510 mg, 2.1 mmol) in dry tetrahydrofuran (10 cm^3) was

added and the reaction stirred for 30 min at 24°C. The reaction mixture was then cooled to -50°C and the cooled mixture treated with methyllithim (1.4 M in diethyl ether, 2.9 cm^3) and stirred at this temperature for 10 min. This mixture was added to copper cyanide (190 mg, 2.1 mmol) in a flame-dried vessel at -50°C and stirred for 15 min. Addition of methyllithium (1.4 M in diethyl ether, 1.5 cm^3) was followed by stirring at -50°C for a further 15 min. A solution of enone **(21)** (300 mg, 4.2 mmol) in dry tetrahydrofuran (3 cm^3) was added and the reaction stirred at the -40°C for a further 1 h, then at ambient temperature for 20 h. The solution was allowed to warm to 0°C before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into ethyl acetate (3 x 15 cm^3) and filtered through Celite before being washed with brine and dried over anhydrous magnesium sulphate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1: 4) yielded **96** (42.8 mg; 4%); δ_H (300 MHz, $CDCl_3$) 0.013 (6H, m, $Si(CH_3)_2$), 0.88 (12H, *t*-Bu + CH_3), 1.22-1.65 (17H, m, 7 x CH_2, CH_3), 2.04 (2H, m, H-4^2), 2.26 (2H, t, *J* 7.4 Hz, -CH_2CO_2-), 2.57 (1H, m, H-5), 2.99 (2H, m, H-2 and H-6), 3.10 (1H, m, H-1), 3.25 (1H, m, H-7), 4.03 (1H, dd, *J* 12.1 and 6.2 Hz, H-5^3), 4.12 (2H, q, *J* 7.1 Hz, -$CO_2CH_2CH_3$-), 5.23-5.36 (1H, H-5^2), 5.45-5.55 (1H, H-5^1), 6.01 (2H, m, H-8 and H-9) and 6.39 (1H, m, H-4^1); (Found M^+ 528.3672; $C_{32}H_{52}O_4Si$ requires 528.3635).

Addition of **2-[5-iodopentyl) oxy] tetrahydro-2H-pyran (87)** to give **97** and **107**

1) Mediated by potassium-*t*- butoxide

The butyl ketone **(82)** (50 mg, 0.25 mmol) in dry dimethylsulfoxide (4 cm^3) was added to a suspension of potassium-*t*- butoxide (34 mg, 0.28 mmol) in

dry dimethylsulfoxide (4 cm^3) at 24°C under an inert nitrogen atmosphere. The mixture was stirred at this temperature for 20 min prior to the addition of **87** (102 mg, 0.34 mmol) in dry dimethylsulfoxide (1 cm^3). Stirring was continued for 2 h after which the reaction was quenched with water and the resulting mixture extracted with ethyl acetate (3 x 15 cm^3). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Column chromatography on silica gel using ethyl acetate-hexane (1:19) as eluent to gave the *cis* addition product **(4-*exo*, 5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97)** as a clear oil (25 mg, 27%); ν_{max}/cm^{-1} 1669 (CO); δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, CH_3), 1.23-1.76 (23 H, m, 10 x CH_2, 2 x H-10, H-5), 1.81 (1H, m, H-4), 2.24 (1H, m, H-6), 2.87 (1H, m, H-7), 3.0 (1H, m, H-2), 3.07 (1H, m, H-1), 3,36 (1H, dt, *J* 2 x 9.0 and 6.4 Hz, H-6'), 3.46-5.54 (1H, m, H-4^5), 3.70 (1H, m, H-6'), 3.85 (1H, m, H-4^5), 4.58 (1H, m, H-2'), 5.96 (1H, dd, *J* 5.7 and 3.2 Hz, H-9) and 6.01 (1H, *J* 5.7 and 3.0 Hz, H-8); δ_C (75 MHZ, $CDCl_3$) 14.1 (CH_3), 19.7 (CH_2), 22.5 (CH_2), 22.7 (CH_2), 25.5 (CH_2), 29.5 (CH_2), 29.8 (C-5), 30.8 (CH_2), 32.6 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 46.1(C-1), 47.2 (C-2), 48.3 (C-7), 48.8 (C-6), 52.3 (CH_2), 54.8 (CH_2), 62.4 (C-6'), 62.9 (CH), 67.5 (C-4^5), 98.9 (C-2'), 135.7 (C-8 or C-9), 136.3 (C-8 or C-9) and 220.9 (CO); (Found M^+ 374.2834 $C_{24}H_{38}O_3$ requires 374.2821); followed by **82** (2.6 mg, 5%) followed by the *trans* addition product **(4-*endo*,5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (107)** as a clear oil (33 mg, 35%); ν_{max}/cm^{-1} 1669 (CO); δ_H (300 MHz, $CDCl_3$) 0.94 (3H, t, *J* 6.9 Hz, CH_3), 1.23-1.59 (23 H, m, 10 x CH_2, 2 x H-10, H-5), 1.93 (1H, m, H-4), 2.54 (1H, m, H-6), 2.97 (1H, m, H-7), 3.00 (1H, m, H-2), 3.10 (1H, m, H-1), 3.36 (1H, dt, *J* 2 x 9.6 and 6.8 Hz, H-6'), 3.49 (1H, m, H-4^5), 3.70 (1H, dt, *J* 2 x 9.6 and 6.9 Hz, H-6'), 3.85 (1H, m, H-4^5), 4.56 (1H, m, H-2'), 6.02 (1H, dd, *J* 5.8 and 3.0 Hz, H-8) and 6.13 (1H, dd, *J* 5.8 and 3.2 Hz, H-9); δ_C (75 MHZ,

$CDCl_3$) 14.1 (CH_3), 19.7 (CH_2), 22.9 (CH_2), 25.5 (CH_2), 26.6 (CH_2), 27.1 (CH_2), 27.4 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 30.8 (CH_2), 36.5 (CH_2), 43.4 (C-5), 44.5 (C-1), 46.5 (C-6), 47.0 (C-7), 52.5 (C-10), 55.3 (C-2), 58.6 (C-4), 62.3 (C-4^5), 67.6 (C-6′), 98.8 (C-2′), 135.5 (C-8), 137.1 (C-9) and 219.6 (CO); (Found M^+ 374.2834 $C_{24}H_{38}O_3$ requires 374.2821).

2) Mediated by potassium hydride

Potassium hydride (35% suspension in mineral oil, 15 mg, 0.38 mmol) was washed with dry hexane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry tetrahydrofuran. **82** in dry tetrahydrofuran was added and the resulting mixture stirred at 0°C for 5 min prior to the addition of **87** (210 mg, 0.70 mmol) in dry tetrahydrofuran (2 cm^3). The mixture was then stirred at ambient temperature for 18 h. The reaction was quenched by the slow addition of water and the aqueous layer extracted with ethyl acetate (3 x 15 cm^3). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was subjected to column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) affording **(4-*exo*, 5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97)** (7.4 mg, 8%).

3) Mediated by sodium hydride

Sodium hydride (60 % suspension in mineral oil, 12 mg, 0.30 mmol) was washed with dry pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry dimethylsulfoxide (2 cm^3). This suspension was heated at 60°C for 1 h and then cooled to

ambient temperature. Butyl ketone **(82)** (50 mg, 0.25 mmol) in dry dimethylsulfoxide (2 cm^3) was added and the mixture stirred for 15 min at this temperature. **87** in dry dimethylsulfoxide was added with stirring. The resultant mixture was stirred for a further 15 min at this temperature, then water was added and the mixture extracted into ethyl acetate (3 x 15 cm^3), dried over anhydrous sodium sulfate and concentrated. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent gave **(4-*exo*, 5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97)** (28 mg, 30%) followed by **82** (20 mg, 40%) followed by **(4-*endo*, 5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (107)** (2.6 mg, 5%).

5-(Tetrahydro-2′-pyranyloxy) pentan-1-ol (101)

To a reaction vessel charged with 1, 5-pentanediol (200 mg, 1.92 mmol) in dichloromethane (10 cm^3), *p*-toluenesulfonic acid (37 mg, 0.192 mmol) and 3, 4-dihydro-*2H*-pyran (0.12 cm^3, 1.3 mmol) was added. The solution was stirred at 24°C for 18 h and the reaction mixture diluted with water. The organic product was extracted into ethyl acetate (3 x 30 cm^3) and dried over anhydrous magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether as eluent (1:1) yielded **1,5-bis(tetrahydro-*2H*-pyran-2-yloxy)pentane (100)** (168 mg, 46%) as a clear oil; ν_{max}/cm^{-1} 1128.0 (COC); δ_H(400MHz, $CDCl_3$) 1.39-1.84 (18H, m, 9 x CH_2), 3.39 (2H, dt, *J* 2 x 9.6 and 6.6 Hz, H-6′), 3.48 (2H, m, H-6′), 3.72 (2H, dt, *J* 2 x 9.6 and 6.75 Hz, H-1 or H-5), 3.86 (2H, m, H-1 and H-5) and 4.6 (2H, dd, *J* 4.7 and 2.5 Hz, H-2′); δ_C (100 MHz, $CDCl_3$) 19.6, 22.95, 25.5, 29.6, 30.8 (C-3′, C-4′, C-5′, C-2, C-3, C-4), 62.2, 67.45 (C-6′, C-1 and C-5) and 98.8 (C-2′); (Found M^+ 272.1981; $C_{15}H_{28}O_4$ requires 272.1988) followed by the alcohol **101** as a clear oil (143 mg, 57%); ν_{max}/cm^{-1} 3683.8 (OH), 1050.9 (COC); δ_H(300 MHz, $CDCl_3$) 1.39-1.84 (12H, m,

6 x CH_2), 3.40 (1H, dt, *J* 2 x 9.6 and 6.4, H-5′), 3.49 (1H, m, H-6′), 3.65 (2H, t, *J* 6.3 Hz, H-1), 3.75 (1H, dt, *J* 2 x 9.8 and 6.6 Hz, H-5), 3.86 (1H, m, H-6′) and 4.57 (1H dd, *J* 4.35 and 2.5 Hz, H-2′); δ_C (75 MHz, $CDCl_3$) 19.7 , 22.5, 25.5, 29.45, 30.8, 32.5 (C-2, C-3, C-4, C-5′, C-4′, C-3′), 63.4 ,62.9, 67.5 (C-6′, C-5, C-1) , 98.95 (C-2′); (Found M^+ 188.1416; $C_{10}H_{20}O_3$ requires 188.1412).

4-(Tetrahydro-2H-pyran-2′-yloxy)pentyl 4″-methylbenzenesulfonate (102)

The alcohol **(101)** (200 mg, 1.06 mmol) was dissolved in dry dichloromethane (5 cm^3) under a nitrogen atmosphere. To the solution was added triethylamine (0.4 cm^3, 3.18 mmol) and the mixture was cooled to 0°C. Tosyl chloride (400 mg, 2.3 mmol) in dry dichloromethane (5 cm^3) was added, the reaction temperature was raised to 24 °C and stirring was continued for 24 h. The mixture was washed with 6 N hydrochloric acid (2 x 10 cm^3) and saturated aqueous sodium carbonate (2 x 20 cm^3). The organic residue was dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:9) as eluent afforded **102** (0.24 g, 80%); 1.40-1.71 (12 H, m, 6 x CH_2), 2.44 (3H, s, CH_3), 3.33 (1H, dt, *J* 2 x 9.6 and 6.3 Hz, H-1), 3.49 (1H, m, H-3′), 3.69 (1H, dt, *J* 2 x 9.6 and 6.6 Hz, H-1), 3.83 (1H, m, H-3′), 4.03 (2H, t, *J* 6.2 Hz, H-5), 4.53 (1H, br, t, *J* 3.6 Hz, H-2′), 7.34 (2H, dd, *J* 8.4 and 0.8 Hz, 2 x Ar) and 7.78 (2H, d, *J* 8.4 Hz, 2 x Ar); δ_C (75 MHz, $CDCl_3$) 19.7 (CH_3), 21.6, 22.3, 25.5, 28.7, 29.1, 30.7 (CH_2), 62.4, 67.1, 70.5 (C-3′, C-1, C-5), 98.9 (C-1′), 127.9, 129.8, 133.3 and 144.6 (4 x Ar-C).

5-Hydroxypentyl 4′-methylbenzenesulfonate (104)

Silver (II) oxide (3.5 g, 15 mmol) [freshly prepared from silver (I) nitrate with sodium hydroxide in water heated to 80-90°C [131]] was added to a solution of 1, 5 pentane diol (1.0 g, 10 mmol) in dichloromethane (30 cm^3), followed by *p*-toluenesulfonic acid (2.1 g, 11 mmol) and potassium iodide (330 mg, 2 mmol). The reaction mixture was stirred at 24°C for 4 h. The mixture was then filtered through silica gel, washed successively with ethyl acetate and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (3:7) yielded the ditosylate **5-{[(4′-methylphenyl) sulfonyl]oxy} pentyl 4″-methylbenzenesulfonate (103)** (271 mg, 7%) as colourless solid; m.p. 71-74°C (from chloroform), (Found: C, 55.1; H, 6.0; S, 15.0; $C_{19}H_{24}O_6S_2$ requires C, 55.3; H, 5.9; S, 15.5); ν_{max}/cm^{-1} 1311.2 (SO_2), 1083.1 (SO_2); δ_H(300 MHz, $CDCl_3$) 1.32-1.40 (2H, m, C*H*$_2$), 1.55- 1.65 (4H, m, 2 x C*H*$_2$), 2.45 (6H, s, 2 x C*H*$_3$), 3.97 (4H, t, *J* 6.5 Hz, 2 x C*H*$_2$-OTs), 7.34 (4H, d, *J* 8.1 Hz, 4 x Ar) and 7.76 (4H, d, *J* 8.1 Hz, 4 x Ar); δ_C (100MHz, $CDCl_3$) 21.7 (CH_3), 21.8 (CH_2), 28.4 (2 x CH_2), 70.2 (2 x C-OTs), 128.1 (4 x Ar), 130.1 (4 x Ar), 133.3 (C-CH_3) and 145.0 (C-SO_2) followed by the monotosylate **104** (2.06 g, 80%) as a colourless oil; ν_{max}/cm^{-1} 3682.9 (OH), 1306.1 (SO_2), 1076.6 (SO_2); δ_H(300MHz, $CDCl_3$) 1.36-1.45 (2H, m, C*H*$_2$), 1.48-1.55 (2H, m, C*H*$_2$), 1.63-1.73 (2H, m, C*H*$_2$), 1.79 (3H, s, C*H*$_3$), 3.60 (2H, t, *J* 6.3 Hz, H-5), 4.03 (2H, t, *J*, 6.3 Hz, H-1), 7.34 (2H, d, *J* 8.3 Hz, H-2′ and H-3′) and 7.80 (2H, d, *J* 8.4 Hz, H-5′ and H-6′); δ_C(100MHz, $CDCl_3$) 21.5 (CH_3), 21.6 (CH_2), 28.55 (CH_2), 31.8 (CH_2), 62.4 (C-5), 70.3 (C-1), 127.8 (C-2′ and C-3′), 129.7 (C-5′ and C-6′), 133.1 (C-4′) and 144.6 (C-1′); (Found M^+ 258.0934; $C_{12}H_{18}O_4S$ requires 258.0926).

5- Iodopentan-1-ol (106)

1) The monotosylate **(105)** (0.875 g, 3.39 mmol) was suspended in acetone (20 cm^3) and sodium iodide (1.02 g, 6.78 mmol) was added. The mixture was refluxed for 18 h, diluted with water and the organic product extracted into ethyl acetate (2 x 15 cm^3), dried over anhydrous

magnesium sulfate and concentrated. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) as eluent yielding **1- Iodo - 5-(2′-(5″-iodopentyloxy) propan-2′-yl) pentane (105)** (218 mg, 14%); ν_{max}/cm^{-1} 1187.0 (CH_2I) 1128.6 (COC); δ_H (400MHz, $CDCl_3$) 1.43-1.52 (4H, m, 2 x CH_2), 1.65 (4H, quintet, *J* 7.0 Hz, 2 x CH_2), 1.85 (4H, quintet, *J* 7.2 Hz, 2 x CH_2), 2.04 (6H, s, 2 x CH_3), 3.19 (4H, t, *J* 7.0 Hz, 2 x CH_2-I) and 4.07 (4H, t, *J* 6.6 Hz, 2 x CH_2-O-); δ_C(100 MHz, $CDCl_3$) 6.65 (2 x CH_2-I), 21.2 (2 x CH_3), 27.1 (2 x CH_2), 27.8 (2 x CH_2), 33.2 (2 x CH_2), 63.3 (2 x CH_2-O-) and 171.4 (C); (Found M^+ 468.0019; $C_{13}H_{26}I_2O_2$ requires 468.0022) followed by the iodoalcohol **(106)** (0.226g, 31%) as an orange oil; ν_{max}/cm^{-1} 3681.9 (OH), 1205.7 (CH_2I); δ_H(400 MHz, $CDCl_3$) 1.4-1.51 (2H, m, CH_2), 1.55-1.62 (2H, m, CH_2), 1.86 (2H, quintet, *J* 7.2 Hz, CH_2), 3.2 (2H, t *J* 7.0 Hz, CH_2), 3.2 (2H, t *J* 7.0 Hz, H-5) and 3.6 (2H, t, *J* 6.4 Hz, H-1); δ_C (75 MHz, $CDCl_3$) 6.6 (C-5), 26.8 (CH_2), 31.6 (CH_2), 33.2 (CH_2) and 62.6 (C-1); (Found M^+ 213.9845 $C_5H_{11}IO$ requires 213.9855).

2) Cerium (III) trichloride heptahydrate (13.5 g, 41.3 mmol) was added to a stirred suspension of 1, 5 pentane diol **(99)** (3 cm^3, 27.5 mmol) and sodium iodide (4.95 g, 33.0 mmol) in acetonitrile (55 cm^3) and the mixture heated to reflux for 5 h. The solution was cooled to ambient temperature and diluted with water. The mixture was extracted with ethyl acetate and the combined organic extracts washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The resulting crude residue (5.2 g) chromatographed on silica gel using ethyl acetate-petroleum ether (1:4) as eluent afforded the iodoalcohol **(106)** (4.1 g, 70%); ν_{max}/cm^{-1} 3681.9 (OH), 1205.7 (CH_2I); δ_H(400 MHz, $CDCl_3$) 1.4-1.51 (2H, m, CH_2), 1.55-1.62 (2H, m, CH_2). 1.86 (2H, quintet, *J* 7.2 Hz, CH_2), 3.2 (2H, t *J* 7.0 Hz, CH_2), 3.2 (2H, t *J* 7.0 Hz, H-5) and 3.6 (2H, t, *J* 6.4 Hz, H-1); δ_C (75 MHz, $CDCl_3$) 6.6 (C-5), 26.8 (CH_2), 31.6

(CH_2), 33.2 (CH_2) and 62.6 (C-1); (Found M^+ 213.9845 $C_5H_{11}IO$ requires 213.9855).

5-Iodo-1-(*t*-butyldimethylsilyloxy)pentane (108)

To a solution of **106** (100mg, 0.47 mmol), triethylamine (7 µl, 0.51 mmol) and 4-dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol) in dry dichloromethane (6 cm^3) was added *t*-butyldimethylsilyl chloride (0.18 g, 1.18 mmol). The solution was stirred at 24°C for 2 h, and the reaction quenched with 1M HCl. The aqueous phase was extracted with hexane (2 x 15 cm^3) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue chromatographed on silica gel with ethyl acetate-petroleum ether (1:9) giving **108** (0.12 g, 78%); δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 x CH_3), 0.89 (9H, s, *t*-Bu), 1.42-1.57 (4H, m, 2 x CH_2), 1.85 (2H, quintet, *J* 7.2 Hz, CH_2), 3.19 (2H, t, *J* 7.0 Hz, CH_2I) and 3.61 (2H, t, *J* 6.2 Hz, CH_2OSi); δ_C (100 MHz, $CDCl_3$) -5.3 (2 x CH_3), 6.9 (CH_2I), 25.9 (*t*-Bu), 26.9 (CH_2), 31.7 (CH_2), 33.4 (CH_2) and 62.8 (CH_2OSi);(Found M^+-TBDMS 212.9776; $C_{11}H_{25}IOSi$ requires 328.0719).

5-Butyl-4-(4^5-*t*-butyldimethylsilyloxy)pent-4^1-yl)-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (109)

Butyl ketone **(82)** (50 mg, 0.25 mmol) in dry dimethylsulfoxide (2 cm^3) was added to a suspension of potassium-*t*- butoxide (34 mg, 0.28 mmol) in dry dimethylsulfoxide 2 cm^3) at 24°C under an inert nitrogen atmosphere. The mixture was stirred at this temperature for 30 min prior to the addition of **108** (115 mg, 0.35 mmol) in dry dimethylsulfoxide (2 cm^3). Stirring was continued for 18 h after which the reaction was quenched with water and the resulting

mixture extracted with ethyl acetate (3 x 10 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the crude material subjected to column chromatography on silica gel using hexane as eluent to yield **109**[1] as a mixture of *cis* and *trans* products (1:3); ν_{max}/cm^{-1} 1278 (c-O) and 1822 (CO); δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, CH_3), 0.07 (3H, s, CH_3), 0.89 (9H, s, *t*-Bu), 1.26-1.77 (overlapping signals), 1.96 (1H, dd, *J* 6.9 and 2.1 Hz, H-4), 2.03-2.21 (1H, m, H-4), 2,24-2.27 (1H, m, H-6), 2.60-2.63 (1H, m, H-6), 2.80 (1H, m, H-7 or H-2), 2.85 (1H, m, H-7 or H-2), 3.02 (1H, m, H-1), 3.13 (1H, m, H-1), 55-3.67 (2H, m, H-45), 3.73-3.83 (2H, m, H-45), 5.92-6.02 (3H, m, 2 x H-8 and H-9 or 2 x H-9 and H-8), 6.14 (1H, s, H-8 or H-9); (Found M^+ 404.3161; $C_{25}H_{44}O_2Si$ requires 404.3111).

[1]Given the complexity of the ^{13}C NMR spectrum due to overlap of signals of the two diastereoisomers, the ^{13}C data is not included

4-Allyl-5-butyltricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (111)

Potassium hydride (35% suspension in mineral oil, 12 mg, 0.30 mmol) was washed with dry hexane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in dry tetrahydrofuran. **82** (50 mg, 0.25 mmol) in dry tetrahydrofuran (2 cm^3) was added and the resulting mixture stirred at 0°C for 5 min prior to the addition of allyl bromide (0.07 cm^3, 0.75 mmol). The mixture was then stirred at ambient temperature for 18 h. The reaction was quenched by the slow addition of water and the aqueous layer extracted with ethyl acetate (3 x 15cm^3). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was subjected to column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) affording the bisallylated product **110** (18 mg, 25%); δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.0 Hz, CH_3), 1.24-1.54 (7H, m, 3 x

CH_2, H-10_a), 1.58-1.62 (1H, dt, *J* 2 x 10.8 and 2.4 Hz, H-10_b), 1.86 (1H, dd, *J* 19.0 and 12.2 Hz, H-4^1), 2.02 (1H, dd, *J* 19.0 and 11.0 Hz, H-4^1), 2.17-2.25 (1H, dddt, *J* 18.8, 8.8 and 1.8 Hz, H-4^1), 2.28-2.36 (1H, dddt, *J* 18.8, 7.2 and 2.0 Hz, H-4^1), 2.47-2.55 (1H, ddd, *J* 14.0, 10.8 and 5.2 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, dd, H 14.0 and 6.0 Hz, H-2), 3.17 (1H, m, H-1), 4.88-5.03 (4H, m, 2 x H-4^3), 5.45-5.69 (2H, m, 2 x H-4^2) , 6.00 (1H, dd, *J* 5.7 and 3.0 Hz, H-8) and 6.12 (1H, dd, *J* 5.7 and 2.7 Hz, H-9); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3), 22.9 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 37.2 (CH_2), 38.0 (CH_2), 44,0 (CH), 44.1 (CH), 46.0 (CH), 47.2 (CH), 52.6 (CH), 54.7 (CH), 60.3 (C-10), 117.0 (C-8 or C-9), 117.9 (C-8 or C-9), 133.4, 135.2, 135.7, 136.8 (2 x C-4^2 and 2 x C-4^3) and 218.9 (CO); (Found M^+ 284.2154; $C_{20}H_{28}O$ requires 284.2140) followed by **111** (15 mg, 25%) δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t *J* 7.2 Hz, CH_3), 1.30-1.55 (3 x CH_2, H-10_b), 1.59 (1H, dt *J* 2 x 8.4 and 1.8 Hz, H-10_a), 1.77 (1H, m, H-5), 2.03-2.11 (1H, m, H-4), 2.18-2.32 (1H, m, H-4^1), 2.58 (1H, m, H-6), 2.92 (1H, dd, *J* 9.8 and 4.6 Hz, H-2), 2.99 (1H, m, H-7), 3.16 (1H, m, H-1), 4.93-5.01 (2H, m, H-4^3), 5.69-5.71 (1H, m, H-4^2), 6.13 (1H, m, H-8 or H-9), 6.18 (1H, dd, *J* 5.6 and 3.2 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_3), 38.2, 39.7, 40.6, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7. 55.1, 56.2 (CH_2), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 (C-4^2 or C-4^3), 136.5 (C-4^2 or C-4^3) and 218.9 (CO); (Found M^+ 244.1839; $C_{17}H_{24}O$ requires 244.1827) followed by **83** (6 mg, 12%).

4, 4-Diallyl-5-butyltricyclo [5.2.1.$0^{2,6}$] dec-8-en-3-one (110)

Butyl ketone **(82)** (50 mg, 0.25 mmol) in dry tetrahydrofuran (2 cm^3) was added to a stirred suspension of potassium hydride (32 mg ,0.80 mmol) in dry tetrahydrofuran (2 cm^3) and the mixture was stirred at 24°C for 1 h. Allyl bromide (0.07 cm^3, 0.75 mmol) was added and stirring continued for 1h. The mixture was slowly transferred to a separating funnel containing water and the aqueous phase extracted into ethyl acetate (2 x 10 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced

pressure. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) yielded **110** (23 mg, 32%); ν_{max}/cm^{-1} 1570 (C=C) and 1734 (CO); δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.0 Hz, CH_3), 1.24-1.54 (7H, m, 3 x CH_2, H-10_a), 1.58-1.62 (1H, dt, *J* 10.8 and 2.4 Hz, H-10_b), 1.86 (1H, dd, *J* 19.0 and 12.2 Hz, H-4^1), 2.02 (1H, dd, *J* 19.0 and 11.0 Hz, H-4^1), 2.17-2.25 (1H, dddt, *J* 18.8, 8.8 and 1.8 Hz, H-4^1), 2.28-2.36 (1H, dddt, *J* 18.8, 7.2 and 2.0 Hz, H-4^1), 2.47-2.55 (1H, ddd, *J* 14.0, 10.8 and 5.2 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, dd, H 14.0 and 6.0 Hz, H-2), 3.17 (1H, m, H-1), 4.88-5.03 (4H, m, 2 x H-4^3), 5.45-5.69 (2H, m, H-4^2) , 6.00 (1H, dd, *J* 5.7 and 3.0 Hz, H-8 or H-9) and 6.12 (1H, dd, *J* 5.7 and2.7 Hz, H-8 or H-9); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3), 22.9 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 37.2 (CH_2), 38.0 (CH_2), 44.0 (CH), 44.1 (CH), 46.0 (CH), 47.2 (CH), 52.6 (CH), 54.7 (CH), 60.3 (C-10), 117.0 (C-8 or C-9), 117.9 (C-8 or C-9), 133.4, 135.2, 135.7, 136.8 (2 x C-4^2 and 2 x C-4^3) and 218.9 (CO); (Found M^+ 284.2154; $C_{20}H_{28}O$ requires 284.2140) followed by **83** (4.6 mg, 9%).

Ethyl-6-iodohexanoate (112)

Sodium iodide (190 mg, 1.2 mmol) was added to a solution of **91** (300 mg, 0.96 mmol) in acetone (20 cm^3). The reaction was refluxed for 18 h rendering a white suspension. This was quenched with saturated aqueous sodium chloride and the organic product extracted into ethyl acetate (2 x 30 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:9) as eluent gave **112** (210 mg g, 83%); δ_H (300 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.1 Hz, CH_3), 1.43 (2H, m, CH_2), 1.64 (2H, quintet, *J* 7.4 Hz, H-3), 1.83 (2H, quintet, *J* 7.2 Hz, CH_2), 2.30 (2H, t, *J* 7.0 Hz, H-6) and 4.12 (2H, q, *J* 7.1 Hz, -$CH_3C\mathit{H}_2$-); δ_C (100 MHz, $CDCl_3$) 6.4 (CH_3), 14.2 (C-6), 23.8 (CH_2), 29.9

(CH_2), 33.1 (CH_2), 34.0 (C-2), 60.2(-CH_3CH_2-) and 173.4 (CO); (Found M^+ 270.0101; $C_8H_{15}O_2I$ requires 270.0116).

Ethyl 6-(5-butyl-3-oxotricyclo{5.2.1.$0^{2,6}$]dec-8en-4-yl)hexanoate (113 and 114)

A solution of **82** (214 mg, 0.80 mmol) in dimethyl sulfoxide (1cm^3) was added to a suspension of potassium-*t*- butoxide (76 mg, 1.1 mmol) in dimethyl sulfoxide (5 cm^3). The resulting suspension was stirred at 25°C for 15 min **112** in dimethyl sulfoxide (1 cm^3) was then added and the reaction stirred at this temperature for 50 min. Water was slowly added to quench the reaction and the mixture was extracted with ethyl acetate (2 x 20 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was purified by chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent to give a mixture of stereoisomers in **113** and **114** (14 mg, 8%); δ_H (300 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.0 Hz, CH_3), 1.24 (3H, t, *J* 7.0 Hz, CH_3), 1.28-1.63 (17H, m, 7 x CH_2, 2 x H-10, H-5), 1.81 (1H, m, H-4), 2.31 (2H, t, *J* 7.6 Hz, -CH_2CO_2-), 2.59-2.64 (1H, m, H-6), 2.87 (1H, m, H-7), 2.93 (1H, ddd, *J* 9.8, 4.6 and 1.8 Hz, H-2). 3.02 (1H, m, H-7), 3.07 (1H, m, H-2), 3.16 (1H, m, H-1), 4.13 (2H, q, *J* 7.0 Hz, -CO_2CH_2-), 5.95 (1H, dd, *J* 5.8 and 3.0 Hz, H-8 or H-9), 6.00(1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9) and 6.14 (2H, m, H-8 and H-9), followed by **115** (19 mg, 11%); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.2 Hz, CH_3), 1.24 (3H, t, *J* 7.2 Hz, CH_3), 1.28-1.63 (17H, m, 7 x CH_2, 2 x H-10, H-5), 1.93 (1H, m, H-4), 2.26 (2H, t, *J* 7.6 Hz, -CH_2CO_2-), 2.54 (1H, ddd, *J* 10.3, 6.0 and 4.0 Hz, H-6), 2.96 (1H, m, H-7), 3.01 (1H, ddd, *J* 10.3, 4.6 and 2.4 Hz, H-2), 3.12 (1H, m, H-1), 4.12 (2H, q, *J* 7.2 Hz, -CO_2CH_2-), 6.02 (1H, dd, *J* 5.6 and

3.2 Hz, H-8 or H-9) and 6.12 (1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 14.2 (CH_3), 22.9 (CH_2), 24.8 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 29.5 (CH_2), 30.0 (CH_2), 34.3 (CH_2), 36.5 (CH_2), 43.4 (CH_2), 44.4 (CH_2), 46.5 (CH), 47.0 (CH), 52.5 (CH), 55.3 (CH), 58.6 (CH), 60.1 (CH), 135.1 (C-8 or C-9), 137.1 (C-8 or C-9), 196.1 (CO) and 219.4 (CO); (Found M^+ 346.2537; $C_{22}H_{34}O_3$ requires 346.2508).

5-Butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97 and 107)

A reaction vessel was charged with copper iodide (260 mg, 1.37 mmol) and flame dried. Dry tetrahydrofuran (4 cm^3) was added and the suspension cooled to 0°C and *n*-butyllithium (2.5 M in hexane, 2.72 mmol) was added slowly. The mixture was stirred at 0°C for 15 min. Enone **(21)** (100 mg, 0.68 mmol) in dry tetrahydrofuran (2 cm^3) was added and the mixture stirred at ambient temperature for 5 min. A separate flame-dried flask was charged with hexamethylphosphoric triamide (20% vol of THF, 1.6 cm^3) and **87** (810 mg, 2.72 mmol) in dry tetrahydrofuran (8 cm^3) at -78°C. This solution was added to the cuprate mixture *via* cannula and the resultant solution stirred at -78°C for 2 h, then at 0°C for 4 h. After 4 days at this temperature and still no further conversion, the reaction mixture was quenched with saturated aqueous ammonium chloride and the mixture extracted with diethyl ether (3 x 20 cm^3). The organic extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude residue was chromatographed on silica gel using ethyl acetate-petroleum ether (1:19) as eluent and yielded a mixture of *cis* and *trans* addition products **5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97 and 107)** (21 mg, 8%) 0.88 (6H, m, 2 x CH_3), 1.27-3.86 (overlapping signals), 4.57 (2H, m, H-2'), 5.95-6.01 (2H, m, H-8 and H-9) and 6.13 (2H, m, H-8 and H-9)*; followed by **82** (41

mg, 30%) followed by the *cis* addition product **(4-*exo*, 5-*exo*)-5-butyl-4-(5'-(tetrahydro-2H-pyran-2"-yloxy)pent1yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (97)** (50 mg, 20%); ν_{max}/cm^{-1} 1669 (CO); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 6.9 Hz, CH_3), 1.21-1.57 (23 H, m, 10 x CH_2, 2 x H-10, H-5), 1.82 (1H, m, H-4), 2.55 (1H, m, H-6), 2.92 (1H, overlapping signals, dd, H-7), 2.96 (1H, m, H-2), 3.13 (1H, m, H-1), 3.36 (1H, m, H-6′), 3.48 (1H, m, H-4^5), 3.71 (1H, m, H-6′), 3.85 (1H, m, H-4^5), 4.55 (1H, m, H-2′) and 6.12 (2H, m, H-8 and H-9); δ_C (75 MHZ, $CDCl_3$) 14.1 (CH_3), 19.7 (CH_2), 22.5 (CH_2), 22.9 (CH_2), 25.5 (CH_2), 29.6 (CH_2), 30.8 (CH_2), 32.6 (CH_2), 36.5 (CH_2), 37.7 (CH_2), 46.5 (C-1), 47.0 (C-2), 48.3 (C-7), 48.8 (C-6), 52.5 (C-10), 55.3 (CH_2), 62.3 (C-6′), 62.9 (CH), 67.6 (C-4^5), 98.8 (C-2′), 135.5 (C-8 or C-9), 137.1 (C-8 or C-9) and 219.6 (CO); (Found M^+ 374.2827 $C_{14}H_{20}O$ requires 374.2821).

*Given the complexity of the ^{13}C NMR spectrum due to overlap of signals of the two diastereoisomers, the ^{13}C data is not included

5-(3'-*t*-Butyldimethylsilylyoxy-1'-oct-1-enyl)-4, -(5-hydroxy-pentyl)-tricyclo[5.2.1.$0^{2.6}$]-deca-8-ene-3-one (116)

p-Toluene sulfonic acid (2.8 mg, 0.015 mmol) was added to a solution of **97** (27.5 mg, 0.074 mmol) in methanol (5 cm^3) and the reaction mixture was stirred at 25°C for 1 h, then at 45°C for 2 h. The solvent was removed *in vacuo* and saturated aqueous ammonium chloride was added. The organic product was extracted with ethyl acetate (2 x 5 cm^3) and the extract dried over anhydrous sodium sulfate and concentrated. Column chromatography of the product on silica gel with ethyl acetate-petroleum ether (1:4) as eluent gave **116** (17 mg, 79%); δ_H ($CDCl_3$) 0.91 (3H, t, *J* 6.9 Hz, CH_3), 1.21-1.69 (18H, m, 7 x CH_2, 2 x H-10, H-4 and H-5), 1.94 (1H, m, OH), 2.56 (1H, m, H-6), 2.93-2.97 (2H, m, H-

2 and H-7), 3.13 (1H, m, H-1), 3.61 (2H, t, *J* 6.6 Hz, H-4^5) and 6.13 (2H, m H-8 and H-9).

5-Butyl-4-(4^5-oxopent-4^1-yl)tricycle[5.2.1.$0^{2,6}$]dec-8-en-3-one (117)

Dess-Martin periodinane (23 mg, 0.050 mmol) was added to a solution of **116** in dichloromethane (4.5 cm^3). The mixture was stirred for 30 min at 25°C after which it was diluted with ether (5 cm^3) , washed with 0.1 M sodium thiosulfate, saturated sodium hydrogen carbonate and water. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Chromatography on silica gel using ethyl acetate-petroleum ether (3:7) afforded the aldehyde quantitatively; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.0 Hz, CH_3), 1.20-1.63 (16H, 6 x CH_2, 2 x H-10, H-4 and H-5), 2.40 (2H, td, *J* 7.3 and 2 x 1.7 Hz, H-4^4), 2.56 (1H, m, H-6), 2.93 (1H, dd, *J* 9.9 and 4.6 Hz, H-2), 2.97 (1H, m, H-7), 3.13 (1H, m, H-1), 6.12 (1H, dd, *J* 5.6 and 2.9 Hz, H-8 or H-9) , 6.15 (1H, dd, *J* 5.6 and 3.1 Hz, H-8 or H-9) and 9.74 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3), 22.1 (CH), 22.9 (CH), 25.5 (CH), 27.1 (CH), 29.7 (CH), 30.9 (CH), 39.6 (CH_2), 43.7 (CH_2), 45.8 (CH_2), 46.2 (CH_2), 46.8 (CH_2), 52.6 (CH_2), 53.5 (CH_2), 135.28 (C-8 or C-9), 136.4 (C-8 or C-9), 202.4 (CHO) and 220.42 (CO).

4-Allyl-5-butyltricyclo [5.2.1.$0^{2,6}$] dec-8-en-3-one (111 and 121)

n-Butyllithium (2,5M in hexane, 0.28 cm^3) was added to dry tetrahydrofuran (4 cm^3) at -78°C. After addition of diethylzinc (1.1M in toluene, 0.65 cm^3), the reaction mixture was stirred at 0°C for 15 min. The solution was recooled to -

78°C and a solution of **21** (100 mg, 0.68 mmol) in dry tetrahydrofuran (4 cm^3) was added over a 60 min period at this temperature. Stirring was continued for a further 15 min. Hexamethylphosphoric triamide (1.18cm^3, 6.8 mmol) was added and stirring continued for another 15 min. Allyl bromide (0.29 cm^3, 3.4 mmol) was added dropwise and the reaction was stirred at -40°C for 10 h, then at ambient temperature for 8 h. The reaction was quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (3 x 10 cm^3), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Column chromatography on silica gel using ethyl acetate-petroleum (1:32) ether as eluent afforded **111** (21.1 mg, 13%); ν_{max}/cm^{-1} 1587(C=C) and 1717(CO); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.2 Hz, CH_3), 1.55-1.61 (8H, m, 3 x CH_2 and H-10_a and H-10_b), 1.67-1.74 (1H, m, H-5), 2.01-2.09 (1H, m, H-4), 2.18-2.33 (2H, m, H-4^1), 2.56-2.60 (1H, ddd, *J* 10.0 and 2 x 4.0 Hz, H-6), 2.91 (1H, dd, *J* 9.8 and 4.6 Hz, H-2), 2.99 (1H, m, H-7), 3.16(1H, m, H-1), 4.91- 5.02 (2H, m, H-4^3), 5.69-5.79 (1H, overlapping signals dddd, H-4^2), 6.11 (1H, dd, *J* 5.6 and 2.8 Hz, H-8 or H-9) and 6.19 (1H, dd, *J* 5.6 and 3.0 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_3), 38.2, 39.7, 40.6, 40.9, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7, 55.1, 56.2 (CH_2), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 (C-4^2 or C-4^3), 136.5 (C-4^2 or C-4^3) and 218.9 (CO); (Found M^+ 244.1839; $C_{17}H_{24}O$ requires 244.1827) followed by **121** (6.3 mg, 4%) δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.4 Hz, CH_3), 1.51-1.53 (7H, m, 3 x CH_2 and H-10_a), 1.56 (1H, dt, *J* 2 x 8.0 and 1.8 Hz, H-10_b), 1.66-1.75 (1H, m, H-5), 2.04-2.09 (1H, H-4), 2.19-2.26 (2H, m, H-4^1), 2.56-2.65 (1H, dddd, *J* 9.0 and 3 x 4.0 Hz, H-6), 2.91 (1H, dd, *J* 9.8 and 4.6 Hz, H-2), 3.01 (1H, m, H-7), 3.16 (1H, m, H-1), 4.91- 5.02 (2H, m, H-4^3), 5.66-5.78 (1H, overlapping signals dddd, H-4^2), 6.14 (1H, dd, *J* 5.8 and 2.8 Hz, H-8 or H-9) and 6.20 (1H, dd, *J* 5.8 and 3.0 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_3), 38.2, 39.7, 40.6, 45.6, 47.1, 49.6, 52.1, 52.7, 53.7. 55.1, 56.2 (CH_2), 115.6 (C-8 or C-9), 116.2 (C-8 or C-9), 135.8 C-4^2 or C-4^3), 136.5 (C-4^2 or C-4^3) and 218.9 (CO); (Found M^+ 244.1839; $C_{17}H_{24}O$ requires 244.1827) followed by **82** (48 mg, 35%).

5-Butyl-4-pent-4-ynltricyclo[5.2.1.$0^{2,6}$]dec-8-en--one (128)

1) The synthesis of triflate (reaction A) and enolate (reaction B) were conducted simultaneously as described below:

Reaction A:

A reaction vessel was charged with dry dichloromethane (3 cm^3) at -25°C under an inert nitrogen atmosphere. Trifluoromethane sulfonic anhydride (1.2 cm^3, 7.1 mmol) was slowly added with stirring followed by mixture of pent-4-yne-1-ol (0.33 cm^3, 3.4 mmol) and triethylamine (0.58 cm^3, 4.1 mmol) in dry dichloromethane (2 cm^3) which was added over a 10 min period. Stirring was continued for 5 min after which the mixture was filtered under nitrogen through anhydrous sodium sulfate and washed with dry hexane. The resulting solution was cooled to -78°C and flushed with nitrogen gas. It was maintained under these conditions until implementation in the reaction B.

Reaction B:

n-Butyllithium (1.6 M in hexane, 1.4 cm^3) was added to a solution of $ZnCl_2$.TMEDA (0.19 g, 0.75 mmol) [prepared from $ZnCl_2$ and TMEDA in dry tetrahydrofuran][75] in dry tetrahydrofuran (3 cm^3) and the mixture stirred at 0°C for 15 min. The reaction mixture was then cooled to -78°C and a solution of enone **21** (100 mg, 0.68 mmol) was added in dry tetrahydrofuran (4 cm^3) over a 40 min period. Stirring was continued at this temperature for 15 min prior to the

addition of HMPA (1.2 cm^3, 6.8 mmol). After another 10 min the triflate (3.4 mmol in hexane) from reaction A was added *via* cannula with the temperature of both solutions being maintained at -78°C. The reaction mixture was then stirred at -40°C for 18 h before being quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (5 x 10 cm^3) and the combined organic phase washed with brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography in petroleum ether gave **128** (17 mg, 9%); δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8 Hz, CH_3), 1.26-1.36 (8H, m, 4 x CH_2), 1.51-1.74 (8H, m, 2 x H-10, 2 x CH_2, H-4 and H-5), 2.72 (1H, ddd, *J* 10.3, 7.4 and 4.3 Hz, H-6), 2.98 (1H, m, H-7), 3.16 (1H, m, H-1), 3.39 (1H, dd, *J* 10.3 and 4.3 Hz, H-2), 3.98 (1H, d, *J* 5.1 Hz, H-4^5), 6.09 (1H, dd, *J* 5.8 and 3.0 Hz, H-8 or H-9) and 6.19 (1H, dd, *J* 5.8 and 2.7 Hz, H-8 or H-9); δ_C (75 MHz, $CDCl_3$) 13.95 (CH_3), 22.8, 29.5, 30.6, 33.9, 34.2, 42.9, 44.2, 45.3, 46.7, 51.8, 53.0, 60.0, 61.0, 68.0, 92.1 ($CHCHCH_2$-), 135.5 (C-9 or C-9), 136.9 (C-8 or C-9) and 218.6 (CO); (Found M^+ 270.1967 $C_{19}H_{26}O$ requires 270.1984)

2) The synthesis of triflate (reaction A) and enolate (reaction B) were conducted simultaneously as described below:

Reaction A:

A reaction vessel was charged with dry dichloromethane (3 cm^3) at -25°C under an inert nitrogen atmosphere. Trifluoromethane sulfonic anhydride (1.2 cm^3, 7.1 mmol) was slowly added with stirring followed by mixture of pent-4-yne-1-ol (0.33 cm^3, 3.4 mmol) and triethylamine (0.58 cm^3, 4.1 mmol) in dry dichloromethane (2 cm^3) which was added over a 10 min period. Stirring was continued for 5 min after which the mixture was filtered under nitrogen through anhydrous sodium sulfate and washed with dry hexane. The resulting solution

was cooled to -78°C and flushed with nitrogen gas. It was maintained under these conditions until implementation in the reaction B.

Reaction B:

n-Butyllithium (1.6 M in hexane, 1.4 cm^3) was added to a solution **146** (135 mg, 0.49 mmol) in dry tetrahydrofuran (3 cm^3) and the mixture stirred at -25°C for 2 h. The reaction mixture was then cooled to -78°C and the triflate (3.92 mmol in hexane) from reaction A was added *via* cannula with the temperature of both solutions being maintained at -78°C. The reaction mixture was then stirred at -40°C for 18 h before being quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (5 x 10 cm^3) and the combined organic phase washed with brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography in petroleum ether gave **128** (17 mg, 13%); δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8 Hz, CH_3), 1.26-1.36 (8H, m, 4 x CH_2), 1.51-1.74 (8H, m, 2 x H-10, 2 x CH_2, H-4 and H-5), 2.72 (1H, ddd, *J* 10.3, 7.4 and 4.3 Hz, H-6), 2.98 (1H, m, H-7), 3.16 (1H, m, H-1), 3.39 (1H, dd, *J* 10.3 and 4.3 Hz, H-2), 3.98 (1H, d, *J* 5.1 Hz, H-4^5), 6.09 (1H, dd, *J* 5.8 and 3.0 Hz, H-8 or H-9) and 6.19 (1H, dd, *J* 5.8 and 2.7 Hz, H-8 or H-9); δ_C (75 MHz, $CDCl_3$) 13.95 (CH_3), 22.8, 29.5, 30.6, 33.9, 34.2, 42.9, 44.2, 45.3, 46.7, 51.8, 53.0, 60.0, 61.0, 68.0, 92.1 ($CHCHCH_2$-), 135.5 (C-9 or C-9), 136.9 (C-8 or C-9) and 218.6 (CO).

(4*E*)-5-*n*-Butyl-4-ethylidenetricyclo[5.2.1.$0^{2,6}$] dec-8-ene-3-one (131)

n-Butyllithium (1.6 M in hexane, 1.0 cm^3) was added to a stirred suspension of copper (I) iodide (160 mg, 0.82 mmol) in diethyl ether (9 cm^3) cooled to -78°C and stirred at this temperature for 3 h. A solution of enone **(21)** (100 mg, 0.68 mmol) in dry diethyl ether (6 cm^3) was added dropwise over 5 min and the

reaction stirred at this temperature for 1.5 h. After addition of acetaldehyde (0.1 cm^3, 2.04 mmol) the reaction mixture was warmed to 0°C and stirring continued for 18 h. The reaction was quenched with saturated aqueous sodium chloride, extracted into diethyl ether (3 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:19) as eluent gave **131** (45 mg, 29%); δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.3 Hz, CH_3), 1.27-1.41 (7H, m, 3 x CH_2, H-10_a), 1.47 (1H, dt, *J* 2 x 8.2 and 2.0, H-10_b), 1.72 (3H, dd, *J* 7.5 and 1.2 Hz, CH_3), 2.40 (1H, m, H-5), 2.52 (1H, ddd, *J* 8.8, 4.4 and 2.0 Hz, H-6), 2.95 (1H, dd, *J* 8.7 and 4.8 Hz, H-2), 3.0 (1H, m, H-7), 3.22 (1H, m, H-1), 5.93 (1H, dd, *J* 5.6 and 2.9 Hz, H-8 or H-9), 5.96 (1H, dd, *J* 5.6 and 2.9 Hz, H-8 or H-9) and 6.36 (1H, qd, *J* 3 x 7.5 and 2.1 Hz, H-4^1); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3), 14.9 (CH_3), 22.8 (CH_2), 29.1 (CH_2), 35.8 (CH_2), 40.3 (C-10), 44.3 (C-5), 47.36 (CH), 47.4 (CH), 51.5 (CH), 53.8 (CH), 131.5 (C-8 or C-9), 133.4 (C-8 or C-9), 135.9 (C-4^1), 145.8 (C-4) and 209.0 (CO).

(4*E*)-5-Butyl-4-hexylidenetricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (132)

n-Butyllithium (1.6 M in hexane, 2.8 cm^3) was added to a solution of $ZnCl_2$-TMEDA (380 mg, 1.51 mmol) in dry tetrahydrofuran (10 cm^3) at 0°C and the mixture was stirred at this temperature for 15 min. The solution was then cooled to - 40°C and the enone **(21)** (200 mg, 1.37 mmol) in dry tetrahydrofuran (6 cm^3) was added portionwise over 20 min. The solution was stirred at - 40°C for 30 min. The aldehyde, hexanal, (685 mg, 6.85 mmol) was then added and the mixture stirred at this temperature for 1 h before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into diethyl ether (3 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using hexane followed by ethyl-acetate-hexane

(3:97) as eluent yielded the dehydrated double addition product **132** (232 mg, 59%); δ_H (400 MHz, $CDCl_3$) 0.90 (6H, m, 2 x CH_3), 1.26-1.43 (14H, m, 7 x CH_2), 1.47 (1H, t, *J* 1.6 Hz, H-10_a or H-10_b), 1.49 (1H, t, *J* 1.6 Hz, H-10_a or H-10_b), 2.01-2.12 (2H, m, H-4^2), 2.40 (1H, m, H-6), 2.50-2.54 (1H, ddd, *J* 8.8, 4.0 and 1.6 Hz, H-5), 2.94-2.98 (1H, dd, *J* 8.8 and 4.8 Hz, H-2), 3.01 (1H, m, H-7), 3.23 (1H, m, H-1), 5.92-5.97 (2H, m, H-8 and H-9) and 6.29 (1H, ddd, *J* 8.4, 7.2 and 2.4 Hz, H-4^1); δ_C (100 MHz, $CDCl_3$) 14.06 (CH_3), 14.1 (CH_3), 22.5 (CH_2), 22.9 (CH_2), 28.4 (CH_2), 29.1(CH_2), 29.3(CH_2), 31.6(CH_2), 36.5 (CH_2), 40.5 (C-5), 44.6 (CH), 47.5 (CH), 51.6 (CH), 53.9 (CH), 133.6 (C-9), 135.9 (C-8) and 137.2 (C-4^1).

Ethyl (5*E*)-6-(5-butyl-3-oxotricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-ylidene)hexanoate (133)

1) *n*-Butyl lithium (1.6 M in hexane, 2.8 cm^3) was added to a solution of $ZnCl_2$-TMEDA (380 mg, 1.51 mmol) in dry tetrahydrofuran (10 cm^3) at 0°C and the mixture was stirred at this temperature for 15 min. The solution was then cooled to - 40°C and the enone **(21)** (200 mg, 1.37 mmol) in dry tetrahydrofuran (6 cm^3) was added portionwise over 20 min. The solution was stirred at - 40°C for 30 min. The aldehyde **95** (1.1 g, 6.85 mmol) was added and the reaction was stirred at this temperature for 1 h before being quenched with saturated aqueous ammonium chloride. The organic product was extracted into diethyl ether (3 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Column chromatography on silica gel using hexane followed by ethyl-acetate-hexane (3:97) as eluent yielded the dehydrated double addition product **133** (160 mg, 34%); δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8 Hz, C*H*$_3$), 1.25 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.30-1.65 (12H, m, 2 x H-10, 5 x CH_2), 2.02-2.14 (2H, m, H-

4^2), 2.28 (2H, t, *J* 7.4 Hz, H-4^5), 2.39 (1H, m, H-5), 2.52 (1H, ddd, *J* 8.8, 4.0 and 1.6 Hz, H-6), 2.96 (1H, dd, *J* 8.9 and 5.0, H-7), 3.0 (1H, m, H-2), 3.23 (1H, m, H-1), 4.12 (2H, q, *J* 7.2 Hz, (CO)-O-CH_2), 5.94 (1H, dd, *J* 11.4, 5.6 and 2.6 Hz, H-8 or H-9), 5.97 (1H, dd, *J* 5.6 and 2.8 Hz,H-8, H-9) and 6.24 (1H, ddd, *J* 8.8, 6.8, 2.2 Hz, H-4^1);δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 22.8 (CH_2), 24.7 (C-4^2), 28.1 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 34.1 (C-4^5), 36.4 (C-10), 40.5 (C-5), 44.3 (C-6), 47.4, (C-1 and C-7), 51.5 (CH_2), 53.8 (C-2), 60.2 (-$CO_2CH_2CH_3$), 133.5 (C-9), 135.9 (C-8 or C-4^1), 136.0 (C-8 or C-4^1), 145.0 (C-4), 173.3 (CO) and 209.2 (CO); (Found M^+-C_6H_5 278.1832; $C_{22}H_{32}O_3$ requires 344.2351).

2) Methyllithium (1.6M in diethyl ether, 0.045 cm^3) was added to a stirred solution of the enol silyl ether **(146)** (20 mg, 0.072 mmol) in dry tetrahydrofuran (2 cm^3) at -20°C and the solution stirred for 1 h. The mixture was warmed to 0°C and the zinc chloride-TMEDA complex (18 mg, 0.072 mmol) [prepared from a saturated solution of zinc chloride salt in THF to which and tetramethyl ethylene diamide was added] was added. The solution was recooled to -20°C and a solution of the aldehyde **95** (68 mg, 0.43 mmol) in dry tetrahydrofuran (2 cm^3) was added. Th reaction was stirred at this temperature for 1.5 h, then saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (3 x 15 cm^3). Flash chromatography of this residue on silica gel with ethyl-acetate-heptane (1:9) as eluent gave **133** (16.1 mg, 65%); δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.6 Hz, CH_3), 1.25 (3H, t, *J* 7.2 Hz, CH_3), 1.29-1.50 (8H, m, 2 x H-10, 3 x CH_2), 1.57-1.65 (4H, m, 2 x CH_2), 2.03-2.13 (2H, m, H-4^2), 2.28 (2H, t, *J* 7.5 Hz, H-4^5), 2.39 (1H, m, H-6), 2.52 (1H, ddd, *J* 8.7, 3.9 and 1.8 Hz, H-5), 2.96 (1H, dd, *J* 8.9 and 5.0, H-2), 3.00 (1H, m, H-7), 3.22 (1H, m, H-1), 4.12 (2H, q, *J* 7.2 Hz, (CO)-O-CH_2), 5.95 (2H, ddd, *J* 11.4, 5.6 and 2.6 Hz, H-8 and H-9) and 6.24 (1H, ddd, *J* 8.7, 6.9, 2.3 Hz,H-4); δ_C (75 MHz, $CDCl_3$) 14.2

(CH_3), 14.2 (CH_3), 22.8 (CH_2), 24.7 (C-4^2), 28.1 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 34.1 (-CH_2(CO_2)-), 36.4 (CH_2), 40.5 (C-5), 44.3 (C-6), 47.4 (C-1 and C-7), 51.5 (CH_2), 53.8 (C-2), 60.2 (CH_3CH_2O(CO)-), 133.5 (C-9), 135.9 (C-8 or C-4^1), 136.1 (C-8 or C-4^1), 145.0 (C-4), 173.3 (CO) and 209.1 (CO); (Found M^+-C_6H_5 278.1926; $C_{22}H_{32}O_3$ requires 344.2351).

Ethyl 6 (5-butyl-3-oxotricyclo[5.2.1.$0^{2,6}$]dec-8-4-yl)hexanoate (140)

A solution of **133** in dry toluene (3 cm^3) was deoxygenated by bubbling nitrogen gas through it for 10 min. Stryker's reagent, Hexa-μ-hydrohexakis(triphenylphosphine) hexacopper complex (120 mg, 0.062 mmol), was added and the reaction was stirred at ambient temperature for 17 h. A further addition of Stryker's reagent (120 mg, 0.062 mmol) and continued stirring did not effect any further change in the reaction. The reaction mixture was opened to air and stirred for 1h before being filtered through Celite, washed with diethyl ether and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl-acetate-petroleum ether (1:9) as eluent gave the reduced product **140** (9 mg, 42%); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.1 Hz, CH_3), 1.25 (3H, t, *J* 7.1 Hz, CH_3), 1.29-1.62 (17H, 7 x CH_2, 2 x H-10 and H-5), 1.94 (1H, m, H-4), 2.27 (2H, t, *J* 7.6 Hz, -CH_2CO_2-), 2.54 (1H, ddd, *J* 10.3, 6.1 and 4.2 Hz, H-6), 2.97 (1H, m, H-7), 3.01 (1H, ddd, *J* 10.3, 4.5 and 2.4 Hz, H-2), 3.13 (1H, m, H-1), 4.12 (2H, q, *J* 7.1 Hz, -$CO_2CH_2CH_3$-), 6.03 (1H, dd, *J* 5.7 and 3.0 Hz, H-8 or H-9) and 6.13 (1H, dd, *J* 5.7 and 2.9 Hz, H-8 or H-9); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 14.2 (CH_3), 22.9 (CH_2), 24.8 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 29.5 (CH_2), 30.0 (CH_2), 34.3 (CH_2), 36.5 (CH_2), 43.4 (CH_2), 44.4 (CH_2), 46.5 (CH), 47.0 (CH), 52.5 (CH), 55.3 (CH), 58.6 (CH), 60.1 (CH), 135.1(C-8 or C-9), 137.1 (C-8 or C-9), 196.1 (CO) and 219.4 (CO); (Found M+ 346.2524; $C_{22}H_{34}O_3$ requires 346.2508).

5-Butyl-4-hexyltricyclo[5.2.1.$0^{2,6}$]dec-8-en-one (141)

A solution of **132** (20 mg, 0.070 mmol) in dry toluene (2 cm^3) was deoxygenated by purging with nitrogen for 10 min. The triphenylphosphine copper hydride hexamer complex (340 mg, 0.062 mmol) was added and the resulting reaction mixture was stirred at ambient temperature for 18 h. The reaction was quenched with water and the mixture extracted with ethyl acetate (3 x 10 cm^3). The extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel using ethyl acetate-hexane (1:9) as eluent afforded the reduced product **141** (12.8 mg, 63%); ν_{max}/cm^{-1} 1731 (CO); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.9 Hz, CH_3), 0.94 (3H, t, *J* 7.1 Hz, CH_3), 1.21-1.36 (17H, m, 8 x CH_2, H-5), 1.44 (1H, br d, *J* 7.8 Hz, H-10_a), 1.58 (1H, dt, *J* 2 x 8.2 and 1.8 Hz, H-10_b), 1.93 (1H, m, H-4), 2.54 (1H, ddd, *J* 10.3, 6.1 and 4.1 Hz, H-6), 2.96 (1H, m, H-7), 3.00 (1H, ddd, *J* 10.3, 4.5 and 2.4 Hz, H-2), 3.13 (1H, m, H-1), 6.02 (1H, dd, *J* 5.8 and 2.9 Hz, H-9) and 6.13 (1H, dd, *J* 5.8 and 2.9 Hz, H-8); δ_C (100 MHz, $CDCl_3$) 14.1 (2 x CH_3), 22.7 (CH_2), 22.95 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 31.8 (CH_2), 36.6 (CH_2), 43.5 (CH_2), 44.5 (CH), 46.6 (CH), 47.1 (CH), 52.5 (CH), 55.3 (CH), 58.7 (CH), 135.5 (C-9) , 137.1 (C-8) and 209.2 (CO); (Found M^+ 288.246; $C_{20}H_{32}O$ requires 288.2453).

Ethyl (6*Z*)-6-(2'-*n*-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (142) and ethyl (6E)-6-(2'-*n*-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (143)

A solution of **133** (80 mg, 0.23 mmol) and maleic anhydride (56 mg, 0.58 mmol) in 1, 2 dichloroethane (2.9 cm^3) was treated with ethylaluminium dichloride (1.0 M solution in hexane, 0.4 cm^3) at ambient temperature. The solution was then stirred at 50°C for 1.5 h and then quenched with saturated aqueous sodium hydrogen carbonate. The organic product was extracted into diethyl ether and the combined organic extract dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel using ethyl-acetate-hexane (1:4) as eluent gave the prostaglandin **ethyl (6*Z*)-6-(2'-*n*-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (142)** (10.2 mg, 16%); δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, CH_3), 1.24 (3H, t, *J* 7.2 Hz, CH_3), 1.28-1.35 (4H, m, 2 x CH_2), 1.441.72 (7H, m, 3 x CH_2), 2.32 (2H, t, *J* 7.4 Hz, H-5), 2.83 (2H, m, H-2), 3.27 (1H, m, H-2'), 4.12 (2H, q, *J* 7.2 Hz, ((CO)-O-CH_2-), 6.01 (1H, br t, *J* 2 x 7.6 Hz, H-6), 6.23 (1H, dd, *J* 6.0 and 1.7 Hz, H-4') and 7.43 (1H, dd, *J* 6.0 and 2.4 Hz, H-3'); δ_C (75 MHz, $CDCl_3$) 13.9 (CH_3), 14.3 (CH_3), 22.9 (CH_2), 24.6 (CH_2), 26.8 (CH_2), 28.5 (CH_2), 28.9 (CH_2), 33.3 (CH_2), 34.1 (C-5), 45.4 (C-2'), 60.2 ((CO)-O-CH_2-), 136.3 (C-6 or C-4'), 139.4 (C-6 or C-4'), 160.3 (C-3') and 198.2 (CO); Found M^+ 278.1908; $C_{17}H_{26}O_2$ requires 278.1882); followed by **Ethyl (6*E*)-6-(2'-*n*-butyl-5'-oxocyclopent-3'-en-1-ylidene) hexanoate (143)** (51.2 mg, 80%); δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1 Hz, CH_3), 1.25 (3H, t, *J* 7.2 Hz, CH_3), 1.44-1.86 (10, m, 5 x CH_2), 2.22-2.30 (1H, m , H-2), 2.31 (2H, t, *J* 7.2 Hz, H-5), 3.48 (1H, m, H-2'), 4.12 (2H, q, *J* 7.2 Hz, ((CO)-O-CH_2-), 6.32 (1H, dd, *J* 6.0 and 2.0 Hz, H-4'), 6.51 (1H, tt, *J* 2 x 7.8 and 2 x 1.8 Hz, H-6) and 7.53 (1H, ddd, *J* 6.0, 2.7 and 0.9 Hz, H-3'); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 14.3 (CH_3), 22.9 (CH_2), 24.8 (CH_2), 28.2 (2 x CH_2), 28.8 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 34.2 (C-5), 43.3 (C-2'), 60.3 ((-$CO_2C$$H_2$-)), 134.8 (C-4' or C-6), 138.4 (C-4' or C-6), 161.9 (C-3'), 169.4 (C-5), 173.4 (CO) 196.9 (CO) and 217.2 (CO); (Found M^+ 278.1882; $C_{17}H_{26}O_2$ requires 278.1882).

(5*E*)-4-Butyl-5-hexylidenecyclopent-2-en-1-one (145) and (5*Z*) -4-butyl-5-hexylidenecyclopent-2-en-1-one (144)

A solution of **132** (80 mg, 0.28 mmol) and maleic anhydride (68 mg, 0.70 mmol) in 1, 2 dichloroethane (2.9 cm^3) was treated with ethylaluminium dichloride (1.0 M solution in hexane, 0.48 cm^3) at ambient temperature. The solution was then stirred at 50°C for 1.5 h and then quenched with saturated aqueous sodium hydrogen carbonate. The organic product was extracted into diethyl ether and the combined organic extract dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel using ethyl-acetate-hexane (1:4) as eluent gave the prostaglandin **(5*Z*) -4-butyl-5-hexylidenecyclopent-2-en-1-one (144)** (7 mg, 11%); ν_{max}/cm^{-1} 1639 (CO) and 1713 (CO); δ_H (300 MHz, $CDCl_3$)0.91 (6H, m, 2 x CH_3), 2.31- 2.3.9 (1H, m, H-2^2), 1.26-1.79 (12H, m, 6 x CH_2), 2.91 (1H, m, H-3), 6.14 (1H, dd, *J* 5.6 and 2.0 Hz, H-5), 6.64 (1H, td, *J* 7.8 and 2 x 2.8 Hz, H-2^1) and 7.63 (1H, dd, *J* 5.6 and 2.8 Hz, H-4); δ_C (75 MHz, $CDCl_3$) followed by **(5*E*)-4-butyl-5-hexylidenecyclopent-2-en-1-one (145)** (41 mg, 67%); ν_{max}/cm^{-1} 1627 (CO) and 1723 (CO); δ_H (300 MHz, $CDCl_3$) 0.90 (6H, m, 2 x CH_3), 1.23-1.37 (8H, m, 4 x CH_2), 1.45-1.89 (4H, m, 2 x CH_2), 2.17-2.35 (2H, m, H-2^2), 3.45-3.50 (1H, ddd. *J* 8.4, 3.9 and 2.1 Hz, H-3), 6.32 (1H, dd, *J* 6.2 and 1.7 Hz, H-5), 6.55 (1H, tt, *J* 2 x 7.8 and 2 x 1.5 Hz, H-2^1) and 7.54 (1H, ddd, *J* 6.2, 2.7 and 1.5 Hz, H-4); δ_C (75 MHz, $CDCl_3$) 13.90 (CH_3), 13.94 (CH_3), 22.5 (CH_2), 22.8 (CH_2), 28.0 (CH_2), 28.3 (CH_2), 29.1 (CH_2), 21.6 (CH_2), 32.1 (CH_2), 43.3 (C-3), 134.8 (C-5 or C-2'), 135.8 (C-5 or C-2'), 161.8 (C-4) and 197.0 (CO).

5-*exo*-*n*-Butyl-3-trimethylsilyloxy-tricyclo [5.2.1.$0^{2.6}$]-deca-4, 8-diene (146)

1) *n*-Butyllithium (1.6 M in hexane, 0.34 cm^3) was added to a heterogenous mixture of copper cyanide (25 mg, 0.27 mmol) in dry tetrahydrofuran (4 cm^3) at -78°C. The mixture was allowed to warm to ambient temperature until the copper cyanide had dissolved and then recooled to -78°C. Enone **(21)** (20 mg, 0.14 mmol) in dry tetrahydrofuran (2 cm^3) was added and the solution was stirred at this temperature for 30 min. Chlorotrimethylsilane (0.02 cm^3, 0.19 mmol) was then added and the solution was stirred at 0°C for 20 min before being quenched with saturated aqueous sodium bicarbonate. The organic product was extracted into diethyl ether (2 x 10 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Flash chromatography of the crude residue on silica gel using ethyl acetate-heptane (1:9) yielded the *enol silyl ether* **(146)** (17.9 mg, 47%); δ_H (300 MHz, $CDCl_3$) 0.21 (9H, s, 3 x CH_3), 0.91 (3H, t, *J* 6.8 Hz, CH_3), 1.21-1.31 (7H, m, 3 x CH_2, H-10_a), 1.51 (1H, br dt, *J* 2 x 8.0 and 1.7 Hz, H-10_b), 1.80 (1H, m, H-6), 2.25 (1H, m, H-5), 2.84-2.86 (1H, m, H-2), 2.88-2.90 (1H, m, H-7), 2.95-3.01 (1H, m, H-1), 4.39 (1H, br m, H-4) and 6.03 (1H, br m, H-8, H-9).

2) The reaction vessel was charged with diisopropylamine (0.5 cm^3, 3.74 mmol) in dry tetrahydrofuran (15 cm^3) and cooled to -78°C. *n*-Butyl lithium (1.6M in hexane, 2.1 cm^3) was added and the reaction stirred for 30 min at -78°C. The alkyl ketone **(82)** (700 mg, 3.4mmol) was added slowly to the reaction mixture which was stirred for a further 30 minutes before addition of chlorotrimethylsilane (1.5 g, 10.2 mmol). Stirring was continued at -78°C for 1 h, then at 24°C for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate (5 cm^3) and the organic material extracted into ethyl acetate (2 x 15 cm^3), dried over magnesium sulfate and evaporated under reduced pressure, Column chromatography on silica gel using ethyl acetate-petroleum ether (1:99)

afforded the *enol silyl ether* **(146)** as a colourless oil (510 mg, 47%); δ_H (300 MHz, $CDCl_3$) 0.21 (9H, s, 3 x CH_3), 0.91 (3H, t, *J* 6.8 Hz, CH_3), 1.21-1.31 (7H, m, 3 x CH_2, H-10_a), 1.51 (1H, br dt, *J* 2 x 8.0 and 1.7 Hz, H-10_b), 2.25 (1H, m, H-6), 1.80 (1H, m, H-5), 2.84-2.86 (1H, m, H-2), 2.88-2.90 (1H, m, H-7), 2.95-3.01 (1H, m, H-1), 4.39 (1H, br m, H-4) and 6.03 (1H, br m, H-8, H-9).

2-Hydroxyethyl 4-methylbenzenesulfonate (148)

Silver (II) oxide (14.8 g, 120.3 mmol) [freshly prepared from silver (I) nitrate with sodium hydroxide in water heated to 80-90°C[131]]is added to a solution of ethylene glycol (7.0g, 109.2 mmol) in dichloromethane (50 cm^3) at ambient temperature, followed by the addition of *p*-toluenesulfonic acid (2.28g, 120.1 mmol) and potassium iodide (1.99 g, 12.0 mmol). The reaction mixture was stirred at this temperature for 4.5 h. The mixture was then filtered through silica gel, washed successively with ethyl acetate and the solvent removed under reduced pressure. The crude material (28.1 g) was chromatographed on silica gel using ethyl acetate-petroleum ether (1:19) and yielded **2-{[(4'-methylphenyl)sulfonyl]oxy}ethyl-4''-methylbenzenesulfonate (149)** (9.3 g, 23%) as a colourless solid; m.p. 122-125°C (from ethyl acetate-hexane); (Found: C, 51.9; H, 5.0; S, 17.0; $C_{16}H_{18}O_6S_2$ requires C, 51.9; H, 4.9; S, 17.3); ν_{max}/cm^{-1} 1424.9 (SO_2), 1031.1 (SO_2) ; δ_H (400MHz, $CDCl_3$) 2.45 (6H, s, 2 x C*H*$_3$), 4.18 (4H, s, 2 x C*H*$_2$), 7.33 (4H, d, *J* 8.3 Hz, 4 x Ar) and 7.73 (4H, d, *J* 8.3 Hz, 4 x Ar); δ_C (400MHz, $CDCl_3$) 21.9 (2 x CH_3), 66.9 (2 x CH_2), 128.2 (4 x Ar), 130.2 (4 x Ar), 132.7 (2 x C-4' and C-4'') and 145.5 (C-1'and C-1'') followed by the monotosylate **148** (16.0g, 68%) as a colourless solid; (Found : C, 50.1; H, 5.2; S, 15.6; $C_9H_{12}O_4S$ requires C, 50.0; H, 5.6; S, 14.8); ν_{max}/cm^{-1} 3576.6 (OH), 1424.9 (SO_2) ,1030.8 (SO_2); δ_H (400 MHz, $CDCl_3$) 2.35 (H, br s, O*H*), 2.4 (3H, s, C*H*$_3$), 3.79 (2H, br m, H-2), 4.12 (2H, t, *J* 4.5 Hz, H-1), 7.34 (2H, d, *J* 8.1

Hz, H-2′ and H-3′) and 7.79 (2H, d, *J* 8.1, H-5′ and H-6′); δ_C(100 MHz, $CDCl_3$) 21.9 (CH_3), 66.9 (C-1), 71.8 (C-2), 128.2 (C-2′ and C-3′), 130.2 (C-5′ and C-6′), 133.2 (C-4′) and 145.5 (C-1′).

5-(3′-*t*-Butyldimethylsilylyoxy-1′-oct-1-enyl)-4-(ethyl alcohol)-tricyclo[5.2.1.$0^{2,6}$]-deca-8-ene-3-one (150)

Methyllithium (1.4 M in diethyl ether, 1.6 cm^3) was added to a solution of crude **147** (250 mg, 0.54 mmol) in dry tetrahydrofuran (2 cm^3) at -78°C. The solution was warmed to -23°C and stirred at this tempearature for 20 min. The mixture was then cooled to -78°C and a solution of the tosylate **(148)** in dry tetrahydrofuran (2 cm^3) was slowly added. Stirring was continued for 10 min at -78°C, then for 10 min at -23°C. The reaction did not proceed to completion after several hours and quenched with saturated aqueous ammonium chloride and the organic product extracted into diethyl ether (2 x 15 cm^3) and dried over anhydrous magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) gave ketone **(94)** (73 mg, 39%) followed by **(150)** (11 mg, 5%); ν_{max}/cm^{-1} 3063 (OH), 1651.9 (CO); δ_H (300 MHz, $CDCl_3$) 0.125 (6H, s, Si(CH_3)$_2$), 0.89 (12H, d, *J* 3.0 Hz, *t*-Bu and CH_3), 1.26-1.65 (15H, m, 6 x CH_2, 2 x H-10, O*H*), 1.74 (1H, m, H-4), 1.94 (1H, dd, *J* 12.9 and 6.5 Hz, H-5), 2.54 (2H, m, H-6 and H-7), 2.76 (1H, m, H-2), 2.86 (1H, m, H-1), 4.01 (1H, dd, *J* 12.3 and 6.4 Hz, H-5^3), 5.34 (1H, dd, *J* 15.4 and 6.5 Hz, H-5^1), 5.48 (1H, ddd, *J* 15.4, 6.4 and 3.2, H-5^2), 6.17 (1H, m, H-9) and 6.44 (1H, dd, *J* 5.4 and 3.0 Hz, H-8); δ_C (75 MHz, $CDCl_3$) -4.7 ($SiCH_3$), -4.1 ($SiCH_3$), 14.0 (CH_3), 22.6 (C-10), 21.7 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 26.0 (*t*-Bu), 31.8 (CH_2), 38.4 (CH_2), 39.5 (C-4), 52.2 (C-7), 52.2 (C-1), 54.8 (C-5), 55.0 (C-6), 58.7 (C-2), 78,8 (C-5^3), 132.9 (C-5^2), 133.1 (C-5^1), 135.2 (C-9),136.9 (C-8) and 216.2 (CO); (Found M^+ 432.3101 $C_{26}H_{44}O_3Si$ requires 432.3060).

5-Butyl-4-(5'-(tetrahydru-2H-pyran-2"-yloxy)pent-1-ylidene)-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (151)

Methyllithium (1.6 M in diethyl ether, 0.05 cm^3) was added dropwise to a solution of the enol silyl ether **(146)** in dry tetrahydrofuran (2 cm^3) at - 20°C and the mixture stirred at this temperature for 30 min. $ZnCl_2$.TMEDA (18 mg, 0.072mmol) [prepared from zinc chloride and tetramethylethylenediamine] was then added and the mixture was stirred at 0°C for 15 min and then re-cooled to - 20°C. The aldehyde **152** (80 mg, 0.29 mmol) in dry tetrahydrofuran (2 cm^3) was added at this temperature and the solution stirred temperature for 1 h at - 20°C before being allowed to warm to 24°C and stirred for a further 6 h. The reaction was quenched with saturated aqueous ammonium chloride, extracted into diethyl ether (2 x 15 cm^3) and dried over anhydrous sodium sulfate. Flash chromatography of the crude residue on silica gel using ethyl acetate-heptate (1:19) as eluent **151** (7.5 mg, 28%); δ_H (300 MHz, $CDCl_3$) 0.92 (3H, *J* 7.1 Hz, CH_3), 1.21-1.61 (16H, m, 8 x CH_2), 2.12 (2H, overlapping signals, 2 x H-4^2), 2.29 (1H, m, H-6), 2.42 1H, ddd, *J* 8.7, 4.1 and 1.6 Hz, H-5), 2.97 (1H, dd, *J* 8.7 and 4.8 Hz, H-7), 3.02 (1H, m, H-2), 3.25 (1H, m, H-1), 3.39 (1H, dt, *J* 2 x 9.7 and 6 Hz, H-4^{9a}), 3.53 (1H, m, H-4^{9b}), 3.73 (1H, m, H-4^{5a}), 3.87 (1H, m, H-4^{5b}), 4.58 (1H, t, *J* 3.3 Hz, H-4^7), 5.97 (2H, m, H-7, H-8) and 6.30 (1H, ddd, *J* 8.6, 6.8 and 2.0 Hz, H-4^1); δ_C (500 MHz, $CDCl_3$) 13.1 (CH_3), 18.6, 21.9, 24.5, 28.0, 28.4, 28.5, 28.7, 29.8, 35.4, 37.4, (CH_2), 39.5 (C-6), 43.3 (C-5), 46.4 (C-2), 50.5(C-1), 52.8 (C-7), 61.3 (C-9^1), 66.2 (C-4^5), 97.9 (O-*C*-O), 134.9, 135.6, 143.8 (C-8, C-9 and C-4^1) and 208.4 (CO); (Found M^+ 372.2664; $C_{24}H_{36}O_3$ requires 372.2660).

5-(Tetrahydro-2H-pyran-2′-yloxy)pentenal (152)

Oxalyl chloride (1.4 cm^3, 16.1 mmol) was added to a solution of dimethyl sulfoxide (2.3 cm^3, 32 mmol) in dry dichloromethane (30 cm^3) at -60°C under nitrogen and the mixture stirred for 15 min. **101** (2.7 g, 14.6 mmol) was added in dry dichloromethane (20 cm^3) and stirring continued for a further 15 min before the addition of triethylamine (10 cm^3, 73 mmol). The mixture was stirred for 15 min allowing it to warm to 24°C, them quenched with 1M HCl and the mixture extracted into dichloromethane (3 x 30cm^3), dried over anhydrous magnesium sulfate and the organic extracts concentrated under reduced pressure. Flash cromatography of the residue on silica gel using ethyl acetate-heptane (3:7) gave the aldehyde **152** (2.27 g, 84%); ν_{max}/cm^{-1} 1642 (CO); δ_H (300 MHz, $CDCl_3$) 1.50-1.83 (10 H, m, 5 x CH_2), 2.48 (2H, td, *J* 2 X 1.4 and 7.1 Hz, H-2), 3.36-3.43 (1H, dt, *J* 2 X 9.7 and 6.1 Hz, H-6′), 3.46-3.56 (1H, m, H-5), 3.72-3.80 (1H, *J* 10.4 and 2 x 6.2 Hz, H-6′), 3.85 (1H, ddd, *J* 10.4, 7.5 and 3.5 Hz, H-5), 4.56 (1H, br t, *J* 3.2 Hz, H-2′) and 9.77 (1H, s, CO*H*); δ_C (100 MHZ, $CDCl_3$) 19.7, 21.7, 25.5, 29.1, 30.8 (C-3′, C-4′, C-5′, C-3, C-4), 62.3, 63.0, 67.0 (C-2, C-5, C-6′), 98.9 (C-2′) and 193.2 (CO); (Found M^+ + Na 209.1; $C_{10}H_{18}O_3Na$ requires 209.1154).

General procedure for cycloadditions of enone HH3 with butadiene (a) thermally induced cycloadditions

Tetracyclo [9.2.1.0.^{2,1}0.^{4,9}] tetradeca- 6, 12-diene-3-one (169)

A solution of the enone **(21)** (100 mg, 0.68 mmol) in dry toluene (4 cm^3) was introduced into a pressure tube and purged with nitrogen. Butadiene was condensed into the tube which was sealed and the mixture was heated at 160°C for 24 h (CAUTION-explosion risk). The tube was cooled to 25°C and

then opened. Observation using TLC indicated only the presence of **21**. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give **21** quantitatively.

General procedure for cycloadditions of enone (21) (b) Lewis-acid-catalysed conditions

An excess of 1, 3 butadiene **(168)** was bubbled through toluene (3 cm^3) under an inert atmosphere at -78°C. A solution of enone **(21)** (100 mg, 0.68 mmol) in toluene (1.5 cm^3) was added to the reaction mixture. The Lewis-acid was slowly added at this temperature and the reaction mixture was allowed to warm to room temperature with stirring for 21 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate and the organic product extracted into ethyl acetate (3 x 25 cm^3). The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to give the cycloadduct **(169)** which was purified on silica gel using ethyl acetate-petroleum ether.

a) The reaction using borontrifluoride-diethylether (0.1 cm^3, 0.68 mmol) as Lewis-acid gave an oil (0.21 g) after workup. Chromatography on silica gel (20 g) using ethyl acetate-petroleum ether (1:32) afforded **etracyclo [9.2.1.$0^{2,1}$0.^{4,9}] tetradeca-6, 12-dien-3-one 169** as a colourless oil (0.024 g, 18%); 1.21(1H, m, H-14_a), 1.60(1H, m, H-14_b), 1.94(1H, m, H-8), 1.99(1H, m, H-5), 2.21(1H,m, H-9), 2.28(1H, m, H-10), 2.32(1H, m, H-5), 2.40(1H, m, H-8), 2.63 (1H, m, H-4), 3.19 (1H, m, H-1), 3.42 (1H, m, H-2), 3.42(1H, m, H-11), 5.78(1H, ddd, *J* 9.5, 4.7 and 1.3 Hz, H-6 or H-7), 5.84(1H, ddd, *J* 9.5, 5.2 and 0.9 Hz, H-7 or H-6), 5.94 (2H, m, H-12 and H-13); δ_C(75 MHz, $CDCl_3$) 27.2 and 31.4 (C-5 and C-8), 46.6, 46.9, 47.4, 47.5, 49.5, 52.3, 54.0, 124.5 and 124.9 (C-6 and C-7), 135.8 and 136.0 (C-12 and C-13), 215.8 (C-7)

b) The reaction using Titanium (IV) chloride (0.28 cm^3, 0.14mmol) as Lewis-acid yielded an oily residue post workup. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) as eluent gave the cycloaddition product **tetracyclo [9.2.1.$0^{2,1}$0.$^{4,\ 9}$] tetradeca-6, 12-dien-3-one 169** as a colourless oil (0.045 g, 33%).

c) The reaction with Tin (IV) chloride (0.28 cm^3, 0.14mmol) as Lewis-acid gave a dark oil after workup. Column chromatography on silica gel with ethyl acetate-petroleum ether (1:32) as eluent yielded **tetracyclo [9.2.1.$0^{2,1}$0.$^{4,\ 9}$] tetradeca-6, 12-dien-3-one 169** as a colourless oil (0.025 g, 18%).

Attempted cycloaddition of 21 with butadiene sulfone under a) thermally induced conditions

Tetracyclo [9.2.1.$0^{2,1}$0.$^{4,\ 9}$] tetradeca- 6, 12-diene-3-one (169)

a) The enone **(21)** (50 mg, 0.34 mmol) was added to a solution of butadiene sulfone (200 mg, 1.70 mmol) in dry toluene (5 cm^3) under nitrogen. The mixture was heated at 110°C for 24 h. There was no conversion of starting material after 24 h as observed by TLC. A further aliquot of butadiene sulfone was added (200 mg, 1.70 mmol) and the solution transferred to a sealed tube and heated at 160°C (oil bath) for further 24 h. No reaction was observed and only starting enone was recovered.

b) A solution of the enone **(21)** (1.00 g, 6.76 mmol) in dry toluene (5 cm^3) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone (1.99 g, 16.9mmol) was added to the tube which was sealed and the mixture was heated at 110°C for 18 h. The tube was cooled to 25°C and then opened.

Observation using TLC indicated only the presence of **21**. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give **21** quantitatively.

c) A solution of the enone **(21)** (212 mg, 1.45 mmol) in dry toluene (5 cm^3) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone (857 mg g, 7.26mmol) was added to the tube which was sealed and the mixture was heated at 150°C for 6 days. The tube was cooled to 25°C and then opened. The toluene was removed under reduced pressure and the crude material chromatographed on silica gel with ethyl acetate-hexane (1:19) as eluent. Attempted separation yielded a mixture of inseparable products and **21** (119 mg, 41%).

Attempted cycloaddition of 21 with butadiene sulfone (170) under a) Lewis-acid induced conditions

A solution of the enone **21** (120 mg, 0.82 mmol) in dry toluene (5 cm^3) was introduced into a pressure tube and purged with nitrogen. Butadiene sulfone (485 mg, 4.11mmol) was added to the tube followed by $ZnCl_2$.TMEDA complex. The tube was then sealed and the mixture was heated at 110°C for 24 h. The tube was cooled to 25°C and then opened. Observation using TLC indicated only the presence of **21**. The solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate-petroleum ether as eluent to give **21** quantitatively.

Tetracyclo [9.2.1.$0^{2,1}$0.^{4,9}] tetradeca-3- hydroxy, 6, 12-diene (164)

A solution of the alcohol **(78)** (1.05 g, 7.2 mmol) and butadiene sulfone **(170)** (1.3 g, 10.8 mmol) in dry toluene was purged with nitrogen and then heated in a sealed tube at 160°C (oil bath) for 2 h. The cooled residue was evaporated

under reduced pressure and the resulting crude residue (1.23 g) chromatographed on silica gel (100 g) using ethyl acetate-petroleum ether (1:9) as eluent gave the cycloadduct **(164)** (1.04 g, 72%); ν_{max}/cm^{-1} 1525 C=C) and 3366 (OH); δ_H (300 MHz, $CDCl_3$) 0.80-1.26 (6H, m, H-4, H-5, H-8 and H-9), 1.42 (1H, d, *J* 2.7 Hz, H-14_a), 1.58 (1H, br dt, H-14_a), 2.60-2.68 (1H, H-10), 2.78 (1H, m, H-11), 3.01 (1H, m, H-1), 3.37 (1H, m, H-2), 3.92 (1H, m, H-3), 5.61 (1H, m, H-6, H-7, H12 or H-13), 5.78 (1H, m, H-6, H-7, H12 or H-13), 5.88 (1H, m, H-6, H-7, H12 or H-13) and 5.98 (1H, m, H-13); δ_C (100 MHz, $CDCl_3$) 29.55 (CH_2), 44.50 (CH_2), 44.84 (CH_2), 45.11 (CH), 50.62 (CH), 50.76 (CH), 51.24 (CH), 54.64 (CH), 84.41 (CH), 84.56 (CH), 132.25, 132.90, 135.43 and 137.66 (C-6, C-7, C-12 and C-13);

Tetracyclo [9.2.1.0.^{2,1}0.^{4,9}] tetradeca- 6, 12-diene-3-one (169)

Dess Martin periodinane (50 mg, 0.12 mmol) was added to a solution of the cycloadduct (16 mg, 0.08 mmol) in dry chloroform at 25° C. The mixture was stirred at 25° C for 5 h, water added and then extracted with dichloromethane (4 x 5 cm^3). The combined organic extracts were washed with saturated aqueous sodium thiosulfate, water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel (2 g) using ethyl acetate-hexane (1:4) as eluent to give the ketone **(169)** (9 mg, 56 %).

Tetracyclo [9.2.1.0.^{2,1}0.^{4,9}] tetradeca- 3, 6, 7-hydroxy- 12-ene (165)

A solution of the cycloadduct **(164)** (55 mg, 0.27 mmol) in acetone: water (5 cm^3, 4:1) was treated with osmium tetroxide (14 mg, 0.05 mmol) followed by *N*-morpholine-*N*-oxide (28 mg, 0.28 mmol). The green/grey solution was stirred at

25° C for 3 h, then saturated aqueous sodium sulfite (5 cm^3) was added and stirring continued for 2 h. The mixture was then extracted with dichoromethane (4 x 10 cm^3), the combined extracts washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material (63 mg) was chromatographed on silica gel (7 g) using ethyl acetate-hexane (1:1) as eluent to give **165** (48 mg, 76 %) as a colourless solid m.p 178 – 181° C (from $CHCl_3$-MeOH); ν_{max}/cm^{-1} 3468 (OH); δ_H ($CDCl_3/D_2O$) 1.00-2.24 (8H, m, H-4, H-5, H-8, H-9 and 2 x H-14), 2.40 – 2.50 (1H, m, H-10), 2.56 (3H, m, OH), 2.47-3.16 (3H, m, H-1, H-2, H-11), 5.09 (2H, m, H-6 and H-7) 5.38 (1H, m, H-3) and 6.07 (2H, m, H13 and H-13);δ_C ($CDCl_3/D_2O$) 36.1 (2 x CH_2), 1, 44.1, 45.5, 45.5, 47.3, 48.8, 48.8, 50.2, 66.6 and 68.5 (C-6 and C-7), 80.1 (C-3), 136.3 and 139.1 (C-12 and C-13).

(4-Hydroxytricyclo[5.2.1.$0^{4a,\ 8a}$]-dec-6-en-[1.2-b]furan-4-yl) acetaldehyde (167)

A solution of the cycloadduct **(164)** (223 mg, 1.10 mmol) in acetone: water (8 cm^3, 4:1) was treated with osmium tetroxide (28 mg, 0.11 mmol) followed by *N*-morpholine-*N*-oxide (112 mg, 1.1 mmol). The green/grey solution was stirred at 25° C for 3 h. The starting material was judged to be consumed by TLC. The acetone was removed *in vacuo* and additional water was added (5 cm^3). The mixture was then extracted with ethyl acetate (5 x 10 cm^3), the combined extracts dried over anhydrous magnesium sulfate. The crude extract was then dissolved in dichoromethane. Lead tetraacetate (488 mg, 1.1 mmol) was then added and the resulting mixture stirred at ambient temperature for 2.5 hours. Water was added and the mixture was extracted with ethyl acetate (4 x 10 cm^3), dried under anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel (7 g) using ethyl acetate-hexane (2:3) as eluent to give **167** (133 mg, 52%);

ν_{max}/cm^{-1} 1252 (C-O), 1688 (CO) and 3385 (OH); δ_H(300 MHz, $CDCl_3/D_2O$) 1.35(1H, m, H-9_a), 1.49 and 1.53 (2H, m, 2 x H-3), 1.70 (1H, m, H-9_b), 2.04 (1H, m, H-3a), 2.41 and 2.47 (2H, each m, 2 x H-4^1), 3.1 6 (1H, m, H-8a), 3.32 (1H, m, H-4), 3.52 (1H, m, H-5), 3.58 (1H, m, H-8), 3.80 (1H, ddd, *J* 10.2, 8.9, 5.0 Hz, H-4a), 5.14 (1H, dd, *J* 6.6 and 4.0 Hz, H-8b), 5.35 (1H, dd, *J* 3.9 and 3.2 Hz, H-2), 5.73 and 5.74 (2H, H-6 and H-7), 9.94 (1H, dd, *J* 3.3 and 2.2 Hz, H-4^2); δ_H (75 MHz, $CDCl_3$) 28.8(C-4^1), 34.5(C-3), 43.9, 46.5, 46.6, 46.9, 48.8, 50.0, 54.2, 77.6 (C-8b), 98.5 (C-2), 136.2 and 136.4 (C-6 and C-7), 202.8 (C-4^2).

(3-*exo*, 4-*exo*)-5-Oxatetracyclo[6.2.1.0.$^{2.7}$0$^{4.6}$]undec-9-en-ol (172)

Vanadium acetyl acetonate (20 mg, 0.8 mmol) was added to a solution of **78** (580 mg, 3.9 mmol) in toluene (4 cm^3), at 24°C. *t*- butylhydrogenperoxide (0.7 cm^3, 5.1 mmol) was added slowly and the solution was refluxed for 40 min. The reaction mixture was allowed to cool and the organic product was extracted into ethyl acetate (3x 15 cm^3) from water. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:1) yielded the *epoxide* **172** as a colourless oil (450 mg, 70%); $\nu_{max/cm}^{-1}$ 1221.7 (COC) and 3019.0 (OH); (Found 164.0810 $C_{19}H_{12}O_2$ requires 164.0837); δ_H (400MHz, $CDCl_3$) 1.31 (1H, br dt, H-11_a), 1.48 (1H, dt, *J* 2 x 8.4 and 1.8 Hz, H-11_b), 1.73 (1H, br s, OH), 2.27 (1H, ddd, *J* 2.4, 4.7 and 7.8 Hz, H-7), 2.90 (1H, m, H-8), 3.00 (1H, br dd, *J* 4.1 and 7.7 Hz, H-2), 3.04 (1H, m, H-1), 3.28 (1H, d, *J* 2.7 Hz, H-6), 3.43 (1H, t, *J* 2.0 x 2.3 Hz, H-4), 3.79 (1H, br s, H-3) and 6.10 (2H, m, H-9 and H-10); δ_C (75MHz), 44.5 (C-7), 45.2 (C-2), 51.2 (C-1), 51.5 (C-11), 53.1 (C-7), 62.8 (C-6), 63.4 (C-4), 74.9 (C-3), 134.8 (C-9) and 135.2 (C-10).

exo-3,5-Dihyroxy tricyclo[5.2.1.$0^{2.6}$]-deca-, 4-8-diene (173)

Lithium aluminium hydride (50 mg, 1.3 mmol) was added to a solution of epoxide **172** (50 mg, 0.3 mmol) in dry tetrahydrofuran (6 cm^3) at 0°C under nitrogen. The reaction mixture was brought to reflux for 2 h. The reaction was quenched with water and the same amount of 15% aqueous sodium hydroxide. The solution was filtered through Celite and washed with ethyl acetate. The organic washings were dried over magnesium sulfate. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:1) yielded the *diol*, (38 mg, 76 %) δ_H (300 MHz, CD_3OD) 1.41 (1H, br dt, H-10_a), 1.55 (1H, dt, *J* 2 x 8.1 and 1.6 Hz, H-10_b), 1.74 (1H, dt, *J* 2 x 11.8 and 8.8 Hz, H-4_{exo}), 2.1 (1H, dt, *J* 2 x 11.8 and 6.0 Hz, H-4_{endo}), 2.70 (2H, m, H-2 and H-6), 2.8 (2H, m, H-1 and H-7), 3.51 (2H, m, H-3 and H-5) and 6.18 (2H, t, *J* 2 x 2.0 Hz, H-8 and H-9), δ_C (100MHz) 29.47 (C-10), 44.5 (C-4), 53.0 (C-1 and C-7), 56.2 (C-2 and C-6), 73.0 (C-3 and C-5) and 136.4 (C-8 and C-9).

(3-*exo*,4-*exo*,5-*endo*)-[3-(Benzyloxy)prop-1-ynyl]tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,4-diol (174)

n-Butyllithium (1.6 M solution in hexane, 0.55 cm^3] was added to a solution of (prop-2-ynyloxy)benzene (49 mg, 0.34 mmol) in tetrahydrofuran (10 cm^3) cooled to -78° C. The mixture was stirred at this temperature for 30 min then epoxy-alcohol **(172)** (50 mg, 0.31 mmol) was added dropwise and stirring continued at – 78° C for 6 h. The solution was allowed to warm to 25° C and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate; the combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-hexane as eluent to give **174** (9.5 mg, 9.5%); δ_H (400 MHz, $CDCl_3$) 1.33 (1H, br d, J 8.2 Hz, H-10), 1.44-1.47 (1H, dt, *J* 2 x

8.1 and 1.8 Hz H-10), 2.08 (2H, br s, 2 x OH), 2.12 (2H, m, H-3 and H-4), 2.82-2.85 (1H, ddd, *J* 8.8, 4.5 and 1.4 Hz, H-6), 2.98-3.01 (2H, m, H-2 and H-7), 3.20 (1H, dd, *J* 8.9 and 4.1 Hz, H-1), 3.73 (1H, ddd, *J* 5.1, 3.0 and 1.5 Hz, H-5), 4.22 (2H, s, -OCH_2), 4.59 (2H, s, -OCH_2), 6.03 (1H, dd, *J* 5.7 and 3.1 Hz, H-8 or H-9), 6.23 (1H, dd, *J* 5.7 and 2.9 Hz, H-8 or H-9) and 7.35 (5H, m, Ph*H*); δ_C (100 MHZ, $CDCl_3$) 45.5 (CH_2), 46.0 (CH), 52.2 (CH), 52.4 (CH), 57.0 (CH), 59.2 (CH), 74.2 C-3 or C-4), 74.3 (C-3 or C-4), 84.3 (OCH_2), 95.3 (OCH_2), 122.9, 128.3, 128.5, 131.6, 133.7 and 137.4 (Ph and C-8 and C-9);

(3-*exo*,4-*exo*,5-*endo*)-5-(1,3-Dioxalane-2-ylmethyl)tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,4-diol (175)

The epoxide **(172)** (0.050 g, 0.30 mmol) was added to a solution of 1, 3 dioxalane, 2-magnesium bromide [prepared from 2-bromomethyl 1, 3 dioxalane (0.1 cm^3, 0.90 mmol) and magnesium turnings (0.023 g, 0.96 mmol)] in tetrahydrofuran (5 cm^3) and the reaction was stirred 24°C for 18 h, followed by heating at 50°C for 8 h. Although complete conversion of the starting epoxide had not been effected at this time, the reaction was quenched with water and the organic product extracted into dichloromethane (2 x 15 cm^3). The combined organic extracts were washed with water and dried over magnesium sulfate. The recovered crude material (0.075 mg) was chromatographed silica gel using ethyl acetate-petroleum ether (2:8) yielded the grignard product **175**; δ_H (400 MHz, CD_3OD) 1.28- 1.42 (2H, m, 2 x H-10), 1.62-1.79 (2H, m, H-5^1), 2.53 (1H, m, H-5), 2.78, 1(H, dd, *J* 8.6 and 4.6, H-6), 2.95 (1H, m, H-7), 3.02 (1H, m, H-1), 3.06 (H, dd, *J* 8.6 and 4.0, H-6), 3.51 (H, br d, *J* 5.4, H-3), 3.86 (2H, t, *J* 9.8, -OCH_2), 3.97 (1H, dd, *J* 9.6 and 5.4, H-4), 4.21 (2H, t, *J* 9.8, -OCH_2), 6.15 (H, dd, *J* 5.6 and 3.0, H-9), 6.27 (1H, t, *J* 1.8, H-5^2), 6.36 (H, dd, *J* 5.6 and 3.0, H-8).

en*do*-3-Hydroxydicyclopentadiene (180)

Di-isobutylaluminium hydride (1.5M solution in toluene, 0.8 8mmol) was added dropwise to a stirred solution of the enone **(21)** (0.1g, 0.68 mmol) in dry toluene at -78°C. After 20 min at this temperature, the reaction mixture was diluted with diethylether (8 cm^3) and then treated with 25% ammonium hydroxide at 0°C. The mixture was then stirred for 2 h at rt before being filtered through Celite. The filtrate was extracted using dichlromethane (2 X 40 cm^3), washed with brine (10 cm^3), dried over magnesium sulfate and concentrated. The crude material was chromatographed on silica gel using ethyl acetate-petroleum ether (1:9) to yield the *endo alcohol* **(180)** (77 mg, 77%) as a colourless solid, m.p. 82-83°C (from chloroform); ν_{max}/cm^{-1} 3599 (OH); δ_H (300 MHz, $CDCl_3$) 1.48 (1H, br d, *J* 8.4, H-10_a or H-10_b), 1.57 (1H, dt *J* 2 x 8.4 and 1.8, H-10_a or H-10_b), 2.89-2.98 (3H, m, H-1, H-6, H-7), 3.29 (1H, dd, *J* 7.2 and 3.9, H-2), 4.67 (1H, br d, *J* 8.1, H-3), 5.59 (2H, s, H-8 and H-9), 5.81 (1H, dd, *J* 5.6 and 3.2, H-5) and 6.15 (1H, dd, *J* 5.7 and 2.4, H-4); δ_C (75 MHz, $CDCl_3$) 44.7 (C-10), 46.9 (C-1), 47.0 (C-7), 52.5 (C-6), 54.0 (C-2), 75.9 (C-3), 133.4 (C-9), 134.6 (C-8), 135.2 (C-5) and 135.2 (C-4). (Found: C, H, N. $C_{10}H_{12}O$ requires C, 81.1%; H, 8.1%).

8-Hydroxy-11-oxatetracyclo [$5.2.1^{1,7}.1^{3,9}.\ 0^{2,6}$] undec-4-ene (183)

m-cpba (90 mg, 0.41 mmol) in chloroform (2 cm^3), was added dropwise to a flask containing *endo alcohol* **(180)** (50 mg, 0.34 mmol) in chloroform (5 cm^3). The reaction mixture was heated to reflux for 3 h, thereafter cooled to 24°C and washed with saturated aqueous sodium bisulfite (15 cm^3), saturated aqueous sodium hydrogen carbonate (3 X 15 cm^3) and brine (15 cm^3). The organic product was dried over anhydrous magnesium sulfate, filtered and

concentrated. The recovered material (44 mg) was chromatographed on silica gel ethyl acetate-pet ether (3:7) to yield the cyclic ether **(183)** (43 mg, 77 %) as a colourless solid; m. p. 110-113°; (Found: C, 73.3; H, 7.4%; $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%); ν_{max} (chloroform)/cm^{-1} 3609 (OH), 1220 (C-O-C); δ_H (400 MHz, $CDCl_3$) 1.85 (H, br d, *J* 10.4 Hz, H-10_a or H-10_b), 1.90 (1H, br s, O*H*), 2.13 (H, m, H-7), 2.23 (H, d, *J* 10.4 Hz, H-10_a or H-10_b), 2.69 (H, m, H-1), 2.90 (H, m, H-6), 2.99 (H, m, H-2), 3.88 (H, s, H-8), 4.06 (H, d, *J* 4.4 Hz, H-9), 4.66 (H, dd, *J* 5.2 and 1.8 Hz, H-3), 5.75 (H, dd, *J* 5.2 and 1.8 Hz, H-5) and 5.91 (H, br dd, *J* 5.2 and 1.8 Hz, H-4); δ_H (75 MHz, $CDCl_3$) 38.7 (C-10), 45.3 (C-7), 46.6 (C-1), 49.8 (C-2), 50.5 (C-6,), 75.6 (C-8), 85.3 (C-3), 90.8 (C-8), 134.4 (C-5) and 134.6 (C-4); (Found: M^+ 164.0141 $C_{10}H_{12}O_2$ requires 164.0837).

8-Acetoxy-11-oxatetracyclo [5.2.$1^{1,7}$.$1^{3,9}$. $0^{2,6}$] undec-4-ene (184)

To a stirred solution of the cyclic ether **(183)** (0.050 g, 0.31 mmol) in pyridine (3 cm^3) was added catalytic dimethylaminopyridine and acetic anhydride (0.044 cm^3, 0.47 mmol). After stirring for 20 h at 24°C, the reaction mixture was washed with 1M HCl (2 x 15 cm^3) and extracted with ethyl acetate (2 X 15 cm^3). The organic product was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated. Column chromatography on silica gel with ethyl acetate-pet ether (3:7) yielded the *acetate* **(184)** (0.034g, 49%); ν_{max}/cm^{-1} 1225.0 (CO) and 1260.5 (COC); δ_H (400MHz, $CDCl_3$) 1.84 (1H, dd, *J* 10.8 and 1.6 Hz, H-10_a), 1.99 (3H, s, CH_3), 2.09 (1H, dt, *J* 2 x 10.8 and 1.6 Hz, H-10_b), 2.24 (1H, dq, *J* 4.2, 2.8 and 2 x 1.6, H-1), 2.70 (1H, t, *J* 4.8, H-7), 2.93 1(H, m, H-6), 3.03 (1H, dt, *J* 8.8, 5.6 and 2 x 3.2, H-2), 4.17 (H, d, *J* 4.8, H-8), 4.70 (H, br s, H-9), 4.70 (H, dd, *J* 5.6 and 2.2, H-3), 5.82 (H, ddd, *J* 6 and 2.4 and 0.8, H-4) and 5.97 (H, dd, *J* 6 and 2.4, H-5) and; δ_C (75MHz, $CDCl_3$) 21.1 (CH_3), 38.8 (C-10), 43.1 (C-1), 46.6 (C-7), 49.7 (C-2), 50.5 (C-6), 78.4 (C-9 or C-8), 85.4 (C-3), 88.0 (C-8 or

C-9), 134.3 (C-5), 134.8 (C-4) and 169.9 (CO); (Found M^+ 206.0947 $C_{12}H_{14}O_2$ requires 206.0943).

Tricyclo [5.2.1.$0^{2,6}$]-deca-3-one (185)

To a solution of **21** (200 mg, 1.37 mmol) in ethyl acetate (10 cm^3) was added 10% palladium suspended on carbon (290 mg, 2 mol %) and the suspension stirred at ambient temperature at atmospheric pressure in the presence of hydrogen gas. After 18 h, the suspension was filtered through Celite and the filtrate evaporated under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) yielded the exhaustively hydrogenated product **185** (0.164g, 80 %) as a colourless solid; ν_{max}/cm^{-1} 1700 (CO), 1176 (C-CO-C); δ_H (400MHz, $CDCl_3$) 1.24-1.54 (6H, m, H-5, H-9 and H-10), 1.8-1.99 (2H, m, H-8), 2.12-2.34 (3H, m, H-4 and H-7), 2.49 (H, dt, *J* 2 x 4.2 and 1.6 Hz, H-1), 2.53 (H, m, H-6) and 2.73 (H, m, H-2); (Found M^+ 150.1038; $C_{10}H_{14}O$ requires 150.1045).

Tricyclo [5.2.1.$0^{2,6}$]-dec-4-ene- 3-one (186)

To a solution of **21** (200 mg, 1.37 mmol) in ethyl acetate (10 cm^3) was added 10% palladium suspended on carbon (290 mg, 2 mol %) and the suspension stirred at ambient temperature at atmospheric pressure in the presence of hydrogen gas. After stirring for 1 h at 24°C, the suspension was filtered through Celite and the solvent removed under reduced pressure. Column chromatography on silica gel using ethyl acetate-petroleum ether (1:19) yielded the exhaustively hydrogenated product **185** (39 mg, 19 %) as a colourless solid; m. p. 85-88°; ν_{max}/cm^{-1} 1700 (CO), 1176 (C-CO-C); δ_H (400MHz, $CDCl_3$) 1.24-1.54 (6H, m, H-5, H-9 and H-10), 1.8-1.99 (2H, m, H-8), 2.12-2.34 (3H, m, H-4 and H-7), 2.49 (H, dt, *J* 4.2 and 2 x 1.6, H-1), 2.53 (H, m, H-6) and 2.73

(H, m, H-2) followed by **186** (130 mg, 64%) as a colourless solid; m. p. 88-91°; $\nu_{max/cm}^{-1}$ 1638.1 (CO); δ_H (300MHz, $CDCl_3$) 1.15 (H, m, H-10_a), 1.41 (H, m, H-10_b), 1.60 (H, dt, *J* 2 x 9.5 and 1.7, H-8), 1.69 (H, dt, *J* 2 x 9.5 and 1.7, H-9), 2.49 (H, m, H-6), 2.57 (H, ddd, *J* 2 x 6.6, and 1.8 Hz, H-2), 2.61 (H, m, H-7), 3.22 (H, m, H-1), 6.08 (H, dd, *J* 7.6 and 1.7 Hz, H-5) and 7.57 (H, ddd, *J* 5.4, 3 and 0.8 Hz, H-4); δ_C (100MHz, $CDCl_3$) 21.4 (C-8 and C-9), 35.15 , 36.3, 38.9, 47.1, 49.3 (C-1, C-2, C-6, C-7, C-10), 131.5 (C-5), 162.7 (C-4) and 209.9 (CO); (Found M^+ 148.0868; $C_{10}H_{12}O$ requires 148.0888).

3-*endo*-Hydroxytricyclo [5.2.1.$0^{2,6}$]-dec-4-ene (187)

Di-isobutylaluminium hydride (1.5 M solution in toluene, 0.59 cm^3) was added to a stirred solution of the enone **(21)** (100 mg, 0.68 mmol) in dry toluene (3 cm^3), the mixture was cooled to -78°C and stirred at that temperature for 20 min, before being allowed to warm to 24°C. The reaction mixture was diluted with diethyl ether (8 cm^3) and treated with saturated aqueous ammonium hydroxide (1 cm^3) at 0°C and subsequently for 2 h at 24°C before being filtered through a Celite pad, extracted with CH_2Cl_2 (2 X 10 cm^3), washed with brine and dried over magnesium sulfate. Chromatography on silica gel using ethyl acetate–petroleum ether (3:7) yielded the *endo* alcohol **(187)** (81 mg, 80%) as a colourless solid; (Found; C, 77.52; H, 9.35; $C_{10}H_{13}O$ requires C, 79.96; H, 9.39 ; ν_{max}/cm^{-1} 3682.2 (OH); δ_H (400MHz, $CDCl_3$) 1.30-1.59 (6H, m, H-8, H-9 and 2 x H-10), 1.61 (H, br s, OH), 2.34 (br m, H-2 and H-6), 2.62 (H, tdd, 2 x 9.2, 4.2 and 1.6 Hz, H-7), 2.83 (H, m, H-1), 4.88 (H, br d, *J* 8.4 Hz, H-3), 5.73 (H, dt, *J*, 5.6 and 2 x 1.8 Hz, H-5) and 5.80 (H, dtd *J* 5.6, 2 x 1.8 and 0.4 Hz, H-4); δ_C (75MHz, $CDCl_3$) 24.3 (C-9), 24.9 (C-8), 38.8 (C-10), 41.0 (C-1), 41.4 (C-7), 47.7 (C-6), 51.1 (C-2), 76.5 (C-3), 133.8 (C-5) and 134.7 (C-4).

(3-*endo*,4-*exo*)-5-oxatetracyclo[6.2.1.$0^{2,7}$.$0^{4,6}$]undec-9-en-3-yl 4-nitrobenzoate (189)

To the epoxide **(172)** (440 mg, 2.68 mmol), dissolved in dry tetrahydrofuran (10 cm^3), was added triphenylphosphine (1.76 g, 6.7 mmol), followed by *p*-nitrobenzoic acid (1.11 g, 6.7 mmol). The solution was cooled to 0° C and then di-isopropylazodicarboxylate (542 mg, 2.68 mmol) was added. The solution was then heated to 60° C for 4h, cooled and added to water (15 cm^3). The mixture was extracted with ethyl acetate (3 x 15 cm^3), the combined extracts washed with saturated aqueous sodium hydrogen carbonate, water and brine. The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give crude epoxy-ester (978 mg). This crude material was chromatographed on silica gel (100 g) using ethyl acetate-hexane (1:9) as eluent to give **189** (680 mg, 81 %) as a colourless solid. m.p 142 - 144°C (from $CHCl_3$-MeOH) δ_H (300 MHz, $CDCl_3/D_2O$) 0.36 (1H, m, H-11_a), 0.72 (1H, m, H-11_b), 2.61 (1H, dddd, *J* 10.2, 4.4 , 1.2, and 1.0 Hz, H-2), 2.70 (1H, dd, *J* 1.3 and 4.5 Hz, H-6), 3.02 (1H, *J* 10.2, 1.2, 1.0, and 1.3 H-7), 3.08 (1H, m, H-8), 3.10 (1H, dd, *J* 5.3 and 4.5 Hz, H-4), 3.30 (1H, m, H-1), 5.64 (1H, ddd, *J* 5.3, 4.4 and 0.6 Hz, H-3), 5.85 (2H, m, H-9 and H-10), 7.45 – 7.68 (4H, m, H-2', H-3', H-5' and H-6'); δ_C(75 MHz, $CDCl_3$) 44.1, 44.1, 46.7 and 46.7 (C-1, C-2, C-7 and C-8), 50.0 (C-11), 57.3 (C-6), 60.2 (C-4), 77.6 (C-3), 128.8, 128.8, 129.1, 129.8, 129.8, 133.5, 133.7 and 136.0 (C-9 and C-10), 165 (C=O)

Payne Rearrangement

The epoxy-ester **(189)** (600 mg, 1.92 mmol) was dissolved in methanol (15 cm^3) and solid potassium carbonate (1.32 g, 9.57 mmol) was added. The mixture was stirred at 25° C for 4 h followed by removal of the methanol under

reduced pressure. The solid material was diluted with water (20 cm^3) and extracted with ethyl acetate (3 x 15 cm^3). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the crude material (324 mg) on silica gel (50 g) using ethyl acetate-hexane (1:4) as eluent gave **(3-*endo*, 4-*exo*)-5-oxatetracyclo[6.2.1.$0^{2,7}$.$0.^{4,6}$]undec-9-en-3-ol (191)** (22 mg, 7 %), δ_H(300 MHz, $CDCl_3/D_2O$) 0.47 (1H, m, H-11_a), 0.55 (1H, m, H-11_b), 2.59 (1H, m, H-2), 2.64 (1H, dd, *J* 4.5 and 0.7 Hz, H-6), 2.83 (1H, *J* 6,6 and 4.5 Hz, H-4), 3.03 (1H, dddd, *J* 10.2, 1.4, 0.9 and 0.7 Hz, H-7), 3.08, (1H, m, H-1), 3.14 (1H, m, H-8), 4.87 (1H, ddd, *J* 6.6, 2.8 and 0.7 Hz, H-3), 5.85 (2H, m, H-9 and H-10); δ_C(75 MHz, $CDCl_3$) 44.5, 44.9, 46.7 and 45.8 (C-1, C-2, C-7 and C-8), 49.9 (C-11), 56.9 (C-6), 61.2 (C-4), 76.6 (C-3), 132.3 and 135.3 (C-9 and C-10) followed by **(3-*exo*, 4-*endo*)-5-oxatetracyclo[6.2.1.$0^{2,7}$.$0.^{4,6}$]undec-9-en-3-ol (190)** (214 mg, 68 %); δ_H (300 MHz, $CDCl_3/D_2O$) 0.55 (1H, m, H-11_a), 0.67(1H, m, H-11_b), 2.62 (1H, m, H-2), 2.63 (1H, dd, *J* 4.5 and 0.7Hz, H-6), 2.81 (1H, *J* 6,6 and 4.5 Hz, H-4), 3.07 (1H, dddd, *J* 10.2, 1.4, 0.9 and 0.7 Hz, H-7), 3.11, (1H, m, H-1), 3.17 (1H, m, H-8), 4.86 (1H, dd, *J* 6.8 and 2.8, H-3), 5.77 (2H, m, H-9 and H-10); δ_C(75 MHz, $CDCl_3$) 44.1, 44.3, 46.7 and 46.9 (C-1, C-2, C-7 and C-8), 48.2 (C-11), 57.1 (C-6), 60.2 (C-4), 77.2 (C-3), 136.0 and 136.7 (C-9 and C-10).

(3-*exo*,4-*endo*,5-*exo*)-[3-(Benzyloxy)prop-1-ynyl]tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,4-diol (192)

n-Butyllithium (1.6 M solution in hexane, 0.68 cm^3) was added to a solution of (prop-2-ynyloxy)benzene (160 mg, 1.1 mmol) in tetrahydrofuran (10 cm^3) cooled to -78° C. The mixture was stirred at this temperature for 30 min then epoxy-alcohol **190** (150 mg, 0.914 mmol) was added dropwise and stirring continued at – 78° C for 6 h. The solution was allowed to warm to 25° C and

then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate; the combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate-hexane as eluent to give **192** (187 mg, 66 %) as a pale yellow oil; ν_{max}/cm^{-1} 2480 (CC) and 3085 (OH); δ_H (300 MHz, $CDCl_3/D_2O$) 1.39 (1H, H-10_a), 1.73 (1H, H-10_b), 2.74 (1H, m, H-2), 2.78 (1H, dd, *J* 9.1 and 8.4 Hz, H-5), 3.44 (1H, ddd, *J* 10.2, 8.4 and 5.1 Hz, H-6), 3.44 (1H, m, H-1), 3.48 (1H, dd, *J* 9.1 and 6.3 Hz, H-4), 3.62 (1H, m, H-7), 4.15 (1H, dd, *J* 6.3 and 4.0 Hz, H-3), 4.25 and 4.30 (2H, each d, *J* 12.5 Hz, H-5^3), 4.44 – 4.46 (2H, m, OCH_2), 5.84 (1H, m, H-8), 5.73 (1H, H-9), 7.21 – 7.31 (5H, Ar-H); δ_C(75 MHz, $CDCl_3$) 43.7(C-1, C-2, C-6 and C-7), 44.1, 46.4, 46.9, 48.8 (C-5), 50.4 (C-10), 62.0 (C-5^3), 73.5 (OCH_2), 80.3 (C-3 and C-4), 80.6, 82.1(C-5^2), 84.0 (C-5^1), 127.7 (Ar-C, C-8 and C-9), 128.1,128.8, 135.6 , 136.0 and 137.5.

5.2 MOLECULAR MODELLING

GAMESS-UK[132] was used for all *ab initio* calculations. Both geometrical minimisations and single point energy calculations were made at the Hartree-Fock level with the STO-3G basis set.

5.3 CRYSTAL STRUCTURE DETERMINATION OF 183

Data were collected at 203K using a Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The strategy for the data collection was evaluated using *COLLECT*.[133] The detector to crystal distance was 40 mm. Exposure times of 40 s per frame and scan widths of 1° were used throughout the data collection. Three sets of data were collected: a 182° Φ-scan and two ω-scans. The data were scaled and reduced using *DENZO-SMN*.[134] Unit cell dimensions were refined on 1291 strong. Well-measured reflections in the θ-

range 3.82° to 27.47° (resolution between 20.00 Å and 0.77 Å). The chiral space group P-1 was chosen on the basis of systematic absences. The structure was solved and refined using SHELX97.[135] Hydrogen atoms were placed in calculated positions and refined as riding atoms. Molecular graphics were generated using *X-SEED*.[136]

Details of the data collection and refinement are given in Table 5.1.
Atomic coordinates for non-hydrogen atoms are listed in Table 5.2.
Selected bond lengths are listed in Table 5.2, and torsion angles on Table 5.4.

Table 5.1 Crystal data and structure refinement for **183**

Empirical formula	$C_{10}H_{12}O_2$
Formula weight	164.20
Temperature	203(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.44550(10) Å α = 91.6800(10) ° b = 7.68250(10) Å β = 94.0380(10) ° c = 8.9664(2) Å γ= 114.4710(10) °
Volume	402.270(12) $Å^3$
Z	2
Calculated density	1.356 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	176
Crystal size	0.30 x 0.20 x 0.10 mm
θ range for data collection	3.82 to 27.47 °
Limiting indices	0<=h<=8, -9<=k<=9, -11<=l<=11
Reflections collected / unique	1829 / 1829 [R(int) = 0.0000]
Completeness to theta = 27.47	99.5 %
Max. and min. transmission	0.9907 and 0.9726
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1829 / 0 / 113

Goodness-of-fit on F^2	1.047
Final R indices [I>2σ(I)]	R1 = 0.0385, wR2 = 0.0908
R indices (all data)	R1 = 0.0473, wR2 = 0.0963
Largest diff. peak and hole	0.299 and -0.158 e.Å^{-3}

Table 5.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **183**. U (eq) is defined as one third of the trace of the orthogonal U^{ij} tensor

	X	Y	Z	U
O(12)	2652(2)	7949(1)	6964(1)	37(1)
O(11)	5495(2)	12708(1)	5616(1)	28(1)
C(1)	3473(2)	11108(2)	5975(1)	26(1)
C(4)	4311(2)	12765(2)	8988(1)	26(1)
C(3)	2924(2)	10591(2)	8586(1)	27(1)
C(6)	7786(2)	14364(2)	7928(2)	30(1)
C(8)	3791(2)	13672(2)	7559(1)	26(1)
C(2)	3905(2)	9964(2)	7271(1)	24(1)
C(7)	5968(2)	14271(2)	6742(1)	26(1)
C(5)	6874(2)	13527(2)	9137(1)	30(1)
C(10)	717(2)	10575(2)	7802(2)	35(1)
C(9)	1925(2)	11958(2)	6625(2)	30(1)

Table 5.3 Selected bond lengths for **183**

Bond	Length (Å)	Bond	Length (Å)
O(12)-C(2)	1.4275(14)	C(3)-H(3)	0.9900
O(12)-H(12)	0.90(2)	C(6)-C(5)	1.3238(19)
O(11)-C(1)	1.4381(14)	C(6)-C(7)	1.5032(18)
O(11)-C(7)	1.4621(14)	C(6)-H(6)	0.9400
C(1)-C(9)	1.5363(17)	C(8)-C(7)	1.5319(17)
C(1)-C(2)	1.5554(17)	C(8)-C(9)	1.5374(17)
C(1)-H(1)	0.9900	C(8)-H(8)	0.9900
C(4)-C(5)	1.5007(18)	C(2)-H(2)	0.9900
C(4)-C(3)	1.5494(16)	C(7)-H(7)	0.9900
C(4)-C(8)	1.5566(16)	C(5)-H(5)	0.9400
C(4)-H(4)	0.9900	C(10)-C(9)	1.5314(19)
C(3)-C(2)	1.5313(16)	C(10)-H(10A)	0.9800
C(3)-C(10)	1.5372(19)	C(10)-H(10B)	0.9800
C(9)-H(9)	0.9900		

Table 5.4 Selected torsion angles for **183**

Bonds	Angle (°)	Bonds	Angle (°)
C(7)-O(11)-C(1)-C(9)	34.62(12)	C(7)-O(11)-C(1)-C(2)	-78.50(11)
C(5)-C(4)-C(3)-C(2)	-47.46(14)	C(8)-C(4)-C(3)-C(2)	65.11(12)
C(5)-C(4)-C(3)-C(10)	-153.22(11)	C(8)-C(4)-C(3)-C(10)	-40.65(11)
C(5)-C(4)-C(8)-C(7)	19.06(11)	C(3)-C(4)-C(8)-C(7)	-103.73(10)
C(5)-C(4)-C(8)-C(9)	130.72(10)	C(3)-C(4)-C(8)-C(9)	7.94(11)
C(10)-C(3)-C(2)-O(12)	-75.96(11)	C(4)-C(3)-C(2)-O(12)	178.38(9)
C(10)-C(3)-C(2)-C(1)	41.83(11)	C(4)-C(3)-C(2)-C(1)	-63.83(12)
O(11)-C(1)-C(2)-O(12)	-139.47(10)	C(9)-C(1)-C(2)-O(12)	105.62(10)
O(11)-C(1)-C(2)-C(3)	105.11(11)	C(9)-C(1)-C(2)-C(3)	-9.80(11)
C(1)-O(11)-C(7)-C(6)	98.91(11)	C(1)-O(11)-C(7)-C(8)	-13.44(12)
C(5)-C(6)-C(7)-O(11)	-99.18(12)	C(5)-C(6)-C(7)-C(8)	13.62(13)
C(9)-C(8)-C(7)-O(11)	-12.37(12)	C(4)-C(8)-C(7)-O(11)	96.95(10)
C(9)-C(8)-C(7)-C(6)	-129.08(10)	C(4)-C(8)-C(7)-C(6)	-19.76(11)
C(7)-C(6)-C(5)-C(4)	-1.03(14)	C(8)-C(4)-C(5)-C(6)	-11.74(13)
C(3)-C(4)-C(5)-C(6)	100.30(13)	C(2)-C(3)-C(10)-C(9)	-56.30(11)
C(4)-C(3)-C(10)-C(9)	56.46(11)	C(3)-C(10)-C(9)-C(1)	50.41(11)
C(3)-C(10)-C(9)-C(8)	-51.88(11)	O(11)-C(1)-C(9)-C(10)	-146.13(10)
C(2)-C(1)-C(9)-C(10)	-25.85(12)	O(11)-C(1)-C(9)-C(8)	-39.75(11)
C(2)-C(1)-C(9)-C(8)	80.54(10)	C(7)-C(8)-C(9)-C(10)	137.56(10)
C(4)-C(8)-C(9)-C(10)	27.75(12)	C(7)-C(8)-C(9)-C(1)	30.78(12)
C(4)-C(8)-C(9)-C(1)	-79.03(10)		

REFERENCES

1. Pryor, W. A., *et al. Lipids* **1976,** *11*, 370.
2. Porter, N. A., Funk, M. O., *et al. J. Org. Chem* **1975,** *40*, 3614.
3. Morrow, J. D., et al. *Proc. Natl. Acad. Sci. U. S. A.* **1990,** *87*, 9383.
4. Takeuchi, A. H., T. *Int. I. Clin. Pharm. Res.* **1987,** *7*, 283
5. Shield, M. J. *Pharmacol. Ther.* **1995,** *65*, 125.
6. Roberts, S.; Santoro, G.; Sickle, E. *Chemistry in Britain* **2001**, 34-36.
7. Santoro, M. G. *Experentia* **1994,** *50*, 1039-1047
8. Amici, C., Palamara, A. T., Garaci, E., Santoro, M. G. *Antiviral Res.* **1992,** *19*, 129.
9. Santoro, M. G. *Trends in Microbiol.* **1997,** *5*, 276.
10. Morimoto, R. I., Sarge, K. D., Abravaya, K. *J. Bio. Chem.* **1992,** *267*, 21987.
11. Conti, C., Mastromarino, P., Tomao, P., De Marco, A., Pica, F., Santoro, M. G. *Antimicrobial Agents Chemother.* **1996,** *40*, 367.
12. Rozero, C., Caratolli, A., De Marco, A., Amici, C., Giorgi, C., Santoro, M. G. *J. Clin. Invest.* **1996,** *97*, 1795.
13. Elia, G., Polla, B., Rossi, A., Santoro, M. G. *Eur. J. Biochem.***1991,** *264*, 736.
14. Suzuki, M., Mori, M., Niwa, T., Hirata, R., Furuta, K., Ishikawa, T., Noyori, R. *J. Am. Chem. Soc* **1997,** *119*, 2376.
15. Roberts II, L. J., Montine, T. J., Markesberg, W. R., Trapper, A. R., Hardy, P., Chemtob, S., Dettbarn, W. D., Morrow, J. D. *J. Biol. Chem* **1998,** *273*, 13605 and references therein.
16. Morrow, J. D., Hill, K. E., Burk, R. F., Nammour, T. M., Badr, K. F., Roberts, L. J., II *Proc. Natl. Acad. Sci. USA* **1990,** *87*, 9383.
17. Rodriguez, A. R., Spur, B. W. *Tet. Lett.* **2002,** *43*, 4575.

18. Kim. S.; Powell, W.; Jocobo, S. H.; Practico, D.; Fitzgerald, G. A.; Maxey, K.; Rokach, J. *Biorg. and Med. Chem. Lett.* **2005,** *15*, 1613.
19. Durand, T.; Cracowski, J.-L.; Guy, A. ; Rossi, J.-C. *Biorg. Med. Chem. Lett.* **2001,** *11*, 2495.
20. Morrow, J. D.; Awad, J. A.; Ravenscraft, M. D.; Marini, G.; Badr, K. F.; Williams, R.; Roberts, L. J., II *J. Lipid Mediators* **1993,** *6*, 417.
21. Mulzer, J. C.; Bats, J.-W. *Tet. Lett.* **2001,** *42*, 2001.
22. Patterson, J. W.; Fried, J. H. *J. Org. Chem.* **1974,** *39*, 2506.
23. Suzuki, M.; Koyano, H.; Morita, Y.; Noyori, R. *Synlett* **1989**, 22.
24. Zhu, J. Y; Klunder, A.; Liu, Z.-Y.; Zwannenburg, B. *Tet. Lett.* **1995,** *51*, 5847.
25. Hodgson, D. M.; Gibbs, A. R. *Synlett* **1997**, 657.
26. Corey, E. J. *Tet. Lett.* **1972**, 107.
27. Kraft, M. E.; Wright, C. *Tet. Lett.* **1992,** *33*, 151.
28. Corey, E. J.; Shih, C.; Shih, N.-Y.; Shimoji, K. *Tet. Lett.* **1984,** *25*, 5013.
29. Mulzer, J. C.; Bats, J.-W. *Tet. Lett.* **2001,** *42*, 2961.
30. Rokach, J. K.; Khanapure, S.; Adiyaman, M.; Schio, L.; Fitzgerald, G.A. *Synthesis* **1998**, 569.
31. Khanapure, S. A.; Khanapure, S.; Schio, L.; Rokach, J. *J. Am. Chem. Soc.* **1991,** *113*, 7815.
32. Lai, S.; Lee, D.; Cha, J. K. *J. Org. Chem* **1999,** *64*, 7213.
33. Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc* **1991,** *113*, 7815.
34. Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem* **1997,** *62*, 194.
35. Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002,** *124*, 12424.
36. Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002,** *124*, 10998.

37. Padukulathan, Z. M., S.; Hwang, S.-W.; Khanapure, S.; Lawson, J.; Fitzgerald, G.; Rokach, J.; Khanapure, S.; Khanapure, S.; Adiyaman, M.; Schio, L.; Fitzgerald, G.A. *J. Am. Chem. Soc.* **1998,** *120*, 11953-11961.

38. Vidari, G., Zanoni, G.; Porta, A.; Casrtonovo, F. *J. Org. Chem.* **2003,** *68*, 6005.

39. Zanoni, G.; Porta, A.; Meriggi, A.; Franzini, M.; Vidari, G. *J. Org. Chem.* **2002,** *67*, 6064.

40. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis* Wiley-Interscience:New York, 1989.

41. Suzuki, M., Morita, Y., Koyana, H., Koga, M., Noyori, R. *Tetrahedron* **1990,** *46*, 4809.

42. Noyori, R., Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984,** *23*, 847.

43. Takano, S., Moriya, M., Tanaka, K., Ogasawara, K. *Synthesis* **1994**, 687.

44. Takano, S. I., K., Takahashi, M., Ogasawara, K. *Synlett* **1991**, 636.

45. Alder, K., Flock, F.H. Chem Ber. 1954, 87, 1916; Rosenblum, M. *J. Am. Chem. Soc.* **1957,** *79*, 3179.

46. Rosenblum, M. *J. Am. Chem. Soc* **. 1957,** *79*, 3179.

47. Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223.

48. Morita, Y., Koyana, H., Koga, M., Noyori, R. *Tetrahedron* **1990,** *46*.

49. Carruthers, W. T., Cracowski, J.-L., Guy, A., Rossi, J.-C. *Comprehensive Organometallic Chemistry*; Pergamon Press:Oxford 1985; Vol. vol 7.

50. Dols, P. P. M. A.; Verstappen, M. M. H.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1993,** *49*, 11353.

51. Clayden, G., Warren and Wothers *Organic Chemistry*; Oxford University Press: Oxford, 2001.

52. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.***1988,** *110*, 4726.

53. Suzuki, M., Yanagisawa, A., Noyori, R. J. *J. Am. Chem. Soc* **1985,** *107*, 3348.

54. Posner, G. H., Lentz, C. M. *J. Am. Chem. Soc.* **1979,** *101*, 934.

55. Suzuki, M.; Koyama, H.; Noyori, R., Suzuki, M. *Bull. Chem. Soc. Jpn.* **2004,** *77*, 259.

56. Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990,** *55*, 1857.

57. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997,** *62*, 7768.

58. Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.***1994,** *116*, 11689.

59. Taylor, R. *Synthesis* **1985**, 364.

60. Sauve, G., Bouzide, A. *Org. Lett.* **2002,** *4*, 2329.

61. Pearson, A. J., Lee, K. *J. Org. Chem* **1994,** *59*, 2304.

62. Miller, J. A., Nunn, M. J. *J. Chem. Soc. Perkin I.* **1976**, 416-.

63. Miyaoka, H., Tamura, M., Yamada, Y. *Tet. Lett.* **2000,** *56*, 8083.

64. Corey, E. J., Wess, G. Xiang, Y. B. Singh, A. K. *J. Am. Chem. Soc.* **1987,** *109*, 4717.

65. Ramsey, B. G. a. I., M.L. *J. Org. Chem.* **1981,** *46*, 179-182.

66. Wade, P. A., Dailey and W. P., Carroll, P.J. *J. Am. Chem. Soc.* **1987,** *109*, 5452.

67. Prashad, M.; Seth, M.; Bhaduri, A. P.; Banerji, A. *Org. Mag. Res.* **1980,** *14*, 74.

68. Hansen, P. E.; Bolvig, S.; Wozniak, K. *J. Mol. Struc.* **2005,** *749*, 155.

69. Chapdelaine. M. J., H., M. *Org React. (N. Y.)* **1990,** *38*, 221.

70. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983,** *48*, 4155.

71. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993,** *58*, 2899.

72. Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990,** *46*, 4809.

73. Milburn, K., Thompson, D. *Tet. Lett.* **1993,** *34*, 7291.

74. Tückmantel, W., Oshima, K., Nozaki, H. *Chem. Ber.* **1986,** *119*, 1581.

75. Harada, T., Hara, D., Hattori, K., Oku, A. *Tet. Lett.* **1988,** *29*, 3821.

76. Decicco, C. P., Grover, P. *J. Org. Chem.* **1996,** *61*, 3534.

77. Terjung, A., Jung, K., Schmidt, R. *Liebigs Ann.* **1996**, 1313.

78. Ross, S. A., Pitié, Meunier, B. *J. Chem. Soc., Pekin Trans.1* **2000**, 571.
79. Gooding, O. W. *Journal of Organic Chemistry* **1990,** *55*, 4209.
80. Watson, R.; Kjonass, R. A. *Tet.Lett.* **1986,** *27* 1437.
81. Snider, B. B., Yang, K. *J. Org. Chem.* **1992,** *57*, 3615.
82. Eddolls, J. P., Iqbal, M., Roberts, S. M., Gabriella Santoro, M. *Tet.* **2004,** *60*, 2539.
83. Burke, S. D., Cobb, J. E. *J. Org. Chem.* **1985,** *50*, 3420.
84. Morita, Y., Suzuki, M., Noyori, R. *J. Org. Chem.* **1989,** *54*, 1787.
85. Tajahashi, T., Nakazawa, M., Kanoh, M., Yamamoto, K. *Tet. Lett.* **1990,** *31*, 7340.
86. Kjonaas, R., Vawter, E. J. *J. Org. Chem.* **1986,** *51*, 3993.
87. Mahoney, W. S., Bretensky, D. M., Stryker, J. M. *J. Am. Soc.* **1988,** *110*, 291.
88. Vondrak, T. P., M. *Collection of Czechoslovak Chemical Communications* **1983,** *48*, 82.
89. Yang, N. C.; Jorgenson, M. J., *Tet. Lett.* **1964,** *19*, 1203.
90. Liotta, D., Barnum, C. S. Saindane, M. *J. Org. Chem.* **1981,** *46*, 4301.
91. Levin, J. I. *Tet. Lett.* **1989,** *30*, 13.
92. Weeden, A. C. B., W.; Disanayaka. *Synthesis* **1983**, 952.
93. Paquette, L. A. B., D.T. *J. Org. Chem.* **1985,** *50,* 4102.
94. Radhakrishna, A. S.; Suri, S. K.; Rao, K. R. K. P.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1990,** *20*, 345.
95. Manzotti, R., Tang, S-Y., Janda, K. *Tet.* **2000,** *56*, 7885.
96. Chen, S.; Janda, K. D. *Tetrahedron* **1998,** *39*, 3943.
97. Iqbal, M., Evans, P. *Tet. Lett.* **2003,** *44*, 5741.
98. Takano, S.; Moriya, M.; Ogasawara, K. *Tet. Lett.* **1992,** *33*, 1909.
99. Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271.
100. Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1989**, 359.

101. Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636.

102. Quinkert, G.; M., d. G.; Bucher, A.; Bats, J. W. D., G. . *Tet. Lett.* **1991,** *132*, 3357.

103. Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002,** *41*, 1668.

104. Takano, S.; Moriya, M.; Ogasawara, K. *Tet. Lett.* **1992,** *33*, 1909.

105. Cookson, R. C.; Henstock, J.; Hudec, J. *J. Am. Chem. Soc.* **1966,** *88*, 1059.

106. Dols, P.; Klunder, A.; Zwannenburg, B. *Tet. Lett.* **1993,** *34*, 3181.

107. Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984,** *49*, 4674.

108. Batey, R.; Thadani, A. N.; Lough, A. *J. Chem. Commun.* **1999**, 474.

109. Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986,** *51*, 3076.

110. Ogasawara, K.; Nakagawa, H.; Sugahara, T. *Tet. Lett.* **2001,** *42*, 4523.

111. Larock, R.; Lee, N. *J. Am. Chem. Soc.* **1991,** *113*, 7815.

112. Bach, R. D.; Estévez, C. M.; Winter, J. E.; Glukhovtsev, M. N. *J. Am. Chem. Soc.* **1998,** *120*, 680.

113. McKittrick, B. A.; Ganem, B. *Tet. Lett.* **1985,** *26*, 4895.

114. Hoveyda, A. H. *Chem. Rev.* **1993**, 1307.

115. Henbest, H. B.; Wilson, R. A. L. *J. Am.Chem. Soc.* **1959**, 1958.

116. Bartlett, P. D. *Rec. Chem. Prog.* **1950,** *11*, 47

117. Hiatt, R. *Oxidation*; Marcel Dekker, New York, N. Y., 1971; Vol. 2, Chapter 3.

118. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, 6136.

119. Martin, T.; Soler, M. A.; Betancort, J. M.; Martin, V. S. *J. Org. Chem.* **1997,** *62*, 1570.

120. Olsen, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990,** *122*, 323.

121. Ganem, B., Wrobel, J. E., Eis, M. J. *J. Am. Chem. Soc.* **1984,** *106*, 3693.

122. Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tet.* **1984,** *40*, 4261.

123. Fang, J.-M.; Chen, M.-Y. *Tetrahedron* **1988,** *29*, 5939.

124. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981,** *103*, 5454.

125. Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989,** *67*, 1206.

126. Tanaka, K.; Ogasawara, K. *Synthesis* **1995**, 1237.

127. Martin, S. F.; Dodge, J. A. *Tet. Lett.* **1991,** *32*, 3017.

128. Loibner, H.; Zibari, E. *Helv. Chim. Acta.* **1977,** *60*, 417

129. Perrin, D. D., Armarego, W. L. F. *Purification of laboratory chemicals, third ed.* ; Pergamon: Oxford, 1988.

130. Takano, S.; Moriya, M.; Tanaka, K.; Ogasawara, K. *Synthesis* **1993**, 687.

131. *Organic Syntheses*; Wiley: New York, 1990; Vol. Collect. Vol. VII.

132. M.F. Guest, I. J. B., H.J.J. van Dam, P. Sherwood, J.M.H. Thomas, J.H. van Lenthe, R.W.A Havenith, J. Kendrick, "The GAMESS-UK electronic structure package: algorithms, developments and applications" *Molecular Physics,* **20 March-20 April 2005,** *103*, 719-747.

133. *COLLECT, Data collection software, Nonius B. V., Delft 2000.*

134. Otwinowski, Z.; Minor, W. *Methods in Enzymology* **1997,** *276*, 307.

135. Sheldrick, G. M. S. *Program for the Refinement of Crystal Structures , University of Gottingen* **1997**.

136. Barbour, L. J. X.-S. *A Graphical Interface to Shelx, University of Missouri, Columbia* **1999**.